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

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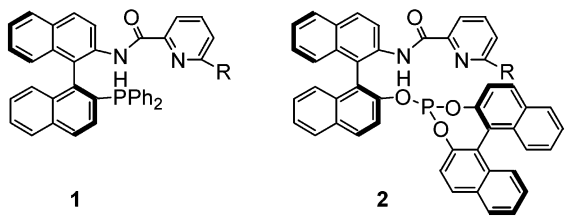
Received May 6, 2003

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 Et_2Zn 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 Et_2Zn addition to cyclic enones. Some diphosphine,[5] diphosphite,[6] P,N ligands,[7] spirophosphoramidites,[8] and aminophosphine[9] are also efficient for this transformation. In contrast to the many successful chiral ligands for Et_2Zn addition to cyclic enones, only a few chiral ligands are reported to be efficient for Et_2Zn 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 En_2Zn addition to chalcones (**1**[10c] and **2**[10a] in Figure 1).



1 **2**

FIGURE 1. Chiral P,N ligands for Cu-catalyzed conjugate addition of Et_2Zn to chalcones.

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 Et_2Zn 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 Et_2Zn 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 Et_2Zn to chalcones (**1**).[10a] Thus **L1** and chalcone were chosen to optimize the reaction conditions. The conjugate addition of Et_2Zn to chalcone was

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10.1021/jo0345897 CCC: $25.00
Published on Web 09/24/2003

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

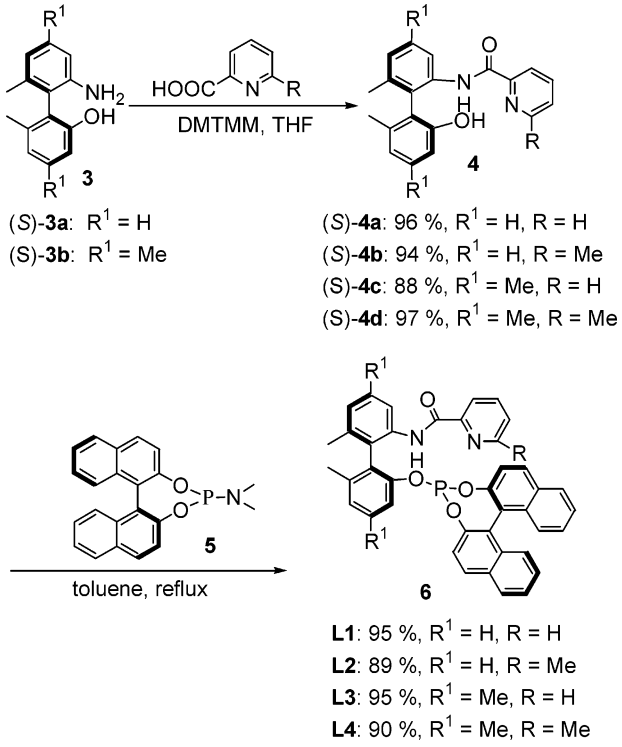
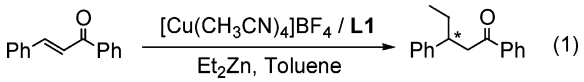


TABLE 1. Cu-Catalyzed Enantioselective 1,4-Conjugate Addition of Et_2Zn to Chalcone[a]



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)/$[Cu(CH_3CN)_4]BF_4$/**L1** = 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 column. [d] The absolute configuration was assigned by comparison of the optical rotation with reported data.

carried out in toluene in the presence of $Cu(CH_3CN)_4BF_4$ (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 Et_2Zn 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 Et_2Zn 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 Et_2Zn 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 Et_2Zn 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.

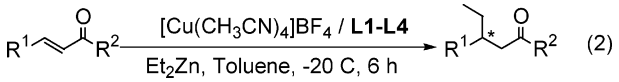
Experimental Section

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; $[\alpha]^{12}_D$ −16.2 (*c* 0.36, $CHCl_3$); ^{1}H 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); ^{13}C 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 $C_{20}H_{18}N_2O_2$ 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; $[\alpha]^{12}_D$ −17.3 (*c* 0.26, $CHCl_3$); ^{1}H 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); ^{13}C 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 $C_{21}H_{20}N_2O_2$ 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; $[\alpha]^{12}_D$ −3.0 (*c* 0.226, $CHCl_3$); ^{1}H 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 Et_2Zn to Acyclic Enones[a]



			L1[b,c]		L2[b,c]		L3[b,c]		L4[b,c]		
entry	R^1	R^2	yield (%)	ee (%)	yield (%)	ee (%)	yield (%)	ee (%)	yield (%)	ee (%)	config[d]
1	Ph	Ph	79	94	76	97	81	96	83	97	*S*
2	4-Me-C_6H_4	Ph	88	95	77	97	90	96	84	97	+[e]
3	Ph	4-Me-C_6H_4	72	90	82	96	87	92	82	97	+[e]
4	4-MeO-C_6H_4	Ph	74	94	68	97	85	96	76	98	*S*
5	Ph	4-MeO-C_6H_4	32	75	23	87	58	84	57	95	−[e]
6	4-Cl-C_6H_4	Ph	74	96	57	94	85	97	77	97	+[e]
7	Ph	4-Cl-C_6H_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_6H_4	Me	24	88	12	54	47	90	28	53	+[e]
10	4-MeO-C_6H_4	Me	24	85	7	40	44	90	21	58	+[e]
11	4-Cl-C_6H_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)/$[Cu(CH_3CN)_4]BF_4$/**L1**−**L4**/Et_2Zn = 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); ^{13}C 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 $C_{22}H_{22}N_2O_2$ 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; $[\alpha]^{26}_D$ −1.6 (*c* 0.322, $CHCl_3$); ^{1}H 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); ^{13}C 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 $C_{23}H_{24}N_2O_2$ 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 chromatagraphy on 30 g of silica gel and eluted with EtOAc/hexanes (1/5−1/2) to afford white foamy solid. Recrystallization with CH_2Cl_2/heptane and drying in vacuo provided 601 mg of ligand **L1** (95%) as a white solid: mp 99−123 °C; $[\alpha]^{16}_D$ 302 (*c* 0.53, THF); ^{1}H NMR (CD_2Cl_2) 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); ^{13}C NMR (CD_2Cl_2) 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; ^{31}P NMR δ 145.34; HR-MS calcd for $C_{40}H_{29}N_2O_4P$ 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; $[\alpha]^{16}_D$ 305 (*c* 0.558, THF); ^{1} H NMR (CD_2Cl_2) 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); ^{13}C NMR (CD_2Cl_2) 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; ^{31}P NMR δ 145.42; HR-MS calcd for $C_{41}H_{31}N_2O_4P$ 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; $[\alpha]^{16}_D$ 261 (*c* 0.508, THF); ^{1}H NMR (CD_2Cl_2) 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); ^{13}C NMR (CD_2Cl_2) 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; ^{31}P NMR δ 145.25; HR-MS calcd for $C_{42}H_{33}N_2O_4P$ 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; $[\alpha]^{16}_D$ 262 (c 0.474, THF); ^{1}H NMR (CD_2Cl_2) 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); ^{13}C NMR (CD_2Cl_2) 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; ^{31}P NMR δ 145.39; HR-MS calcd for $C_{43}H_{35}N_2O_4P$ 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 $[Cu(CH_3CN)_4]BF_4$ (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 CH_2Cl_2 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 Et_2Zn (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 $NaHCO_3$ 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.

Acknowledgment. This work was supported by the National Science Foundation of China (29933050) and the Young Faculty Research Fund of DICP.

Supporting Information Available: General Experimental Section, HPLC and GC conditions for ee values, and spectra of **4a**−**d**, **L1**−**4** (^{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.

JO0345897