JOC Article

Chiral Lewis Acid-Catalyzed Asymmetric Baylis−Hillman Reactions

Kung-Shuo Yang, Wei-Der Lee, Jia-Fu Pan, and Kwunmin Chen*

Department of Chemistry, National Taiwan Normal University, Taipei, Taiwan 116, ROC

kchen@scc.ntnu.edu.tw

Received August 14, 2002

An effective chiral Lewis acid-catalyzed asymmetric Baylis−Hillman reaction is described. Good to high enantioselectivities were obtained using 3 mol % chiral catalyst. Novel camphor-derived dimerized ligands were prepared from the condensation of (+)-ketopinic acid with the corresponding diamines and hydrazine under acidic conditions. When α-naphthyl acrylate was used as a Michael acceptor, the reaction is complete within 20 min with high stereoselectivity and in reasonable chemical yields.

The use of catalytic asymmetric reactions for the synthesis of enantiomerically pure compounds has been an ongoing effort of organic chemists. The coupling of an α,β-unsaturated carbonyl/nitrile with an aldehyde (Baylis−Hillman reaction) produces a useful functionalized acrylate that allows for further functional group manipulation.[1] The reaction is mediated by a tertiary amine, and 1,4-diazabicyclo[2.2.2]octane (DABCO) is the most commonly used catalyst. Although the diastereoselective Baylis−Hillman reaction has been shown to proceed, in some cases, with high to excellent diastereoselectivities,[2] the enantioselective variation of this reaction is less well developed.[3] Recently, Hatakeyama et al. reported that a high to excellent enantiomeric excess can be achieved when quinidine derivatives are used as chiral amine catalysts.[4] The use of a chiral Lewis acid to catalyze this transformation is a common strategy. Aggarwal and coworkers reported on the use of lanthanides and group III metal triflates to accelerate the Baylis−Hillman reaction.[5] However, only 5% ee was obtained when these metals were complexed with a broad range of oxygen-rich chiral ligands. No practical levels of enantioselectivity have yet been reported when a chiral Lewis acid catalyst is used.

The stereocontrol elements for achieving enantioselective carbon−carbon bond formation rely on the proper choice of metal and chiral ligands on suitable substrates. The design and synthesis of a tunable chiral ligand around a Lewis acid metal center constitutes an important issue in the field of asymmetric synthesis.[6] The donor atoms of a ligand would be expected to moderate the Lewis acidity of the metal and subsequently affect the Lewis acid capability toward activation. On the other hand, the structure of the starting substrate may also play an important role (steric and stereoelectronic effects, for example) in influencing the asymmetric outcome. Thus, the importance of incorporating donor group functionality into a ligand molecule is clear. Only a few ligands, to the best of our knowledge, possess a free carboxylic acid functionality.[7] The carboxylic acid moiety may serve as a good donor group by taking advantage of the oxophilic nature of the metal. In continuation of our research interest in the catalysis of such reactions, we report here that practical levels of enantioselectivity can be achieved using camphor-derived dimerized ligands **1**−**4** in the asymmetric Baylis−Hillman reaction.

Results and Discussion

Novel dimerized ligands **1**−**4** can be prepared from the condensation of (+)-ketopinic acid with the corresponding diamines and hydrazine under acidic conditions. Chiral ligands **1** and **4** can be easily synthesized (69 and 88%, respectively) using ethylenediamine and hydrazine in the

* To whom correspondence should be addressed. Phone: 886(2)-89315831. Fax: 886(2)29324249.

(1) For reviews of the Baylis−Hillman reaction, see: (a) Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049. (b) Ciganek, E. *Org. React.* **1997**, *51*, 201. (c) Basavaiah, D.; Rao, D. P.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001. (d) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653.

(2) (a) Kundig, E. P.; Xu, L. H.; Romanens, P.; Bernardinelli, G. *Tetrahedron Lett.* **1993**, *34*, 7049. (b) Yang, K.-S.; Chen, K. *Org. Lett.* **2000**, *2*, 729.

(3) (a) Brzezinski, L. J.; Rafel, S.; Leahy, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 4317. (b) Barrett, A. G. M.; Cook, A. S.; Kamimura, A. *J. Chem. Soc. Chem. Commun.* **1998**, 2533. (c) Hayase, T.; Shibata, T.; Soai, K.; Wakatsuki, Y. *J. Chem. Soc., Chem. Commun.* **1998**, 1271. (d) Oishi, T.; Oguri, H.; Hirama, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1241. (e) Iwabuchi, Y.; Sugihara, T.; Esumi, T.; Hatakeyama, S. *Tetrahedron Lett.* **2001**, *42*, 7867. (f) Iwabuchi, Y.; Furukawa, M.; Esumi, T. Hatakeyama, S. *Chem. Commun.* **2001**, 2030.

(4) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. J. *Am. Chem. Soc.* **1999**, *121*, 10219.

(5) (a) Aggarwal, V. K.; Mereu, A.; Tarver, G. J.; McCague, R. *J. Org. Chem.* **1998**, *63*, 7183. (b) Aggarwal, V. K.; Tarver, G. J.; McCague, R. *J. Chem. Soc., Chem. Commun.* **1996**, 2713.

(6) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.

(7) (a) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993. (b) Barrett, A. G. M.; Kamimura, A. *J. Chem. Soc., Chem Commun.* **1995**, 1755. (c) Ishihara, K.; Kondo, S.; Yamamoto, H. *J. Org. Chem.* **2000**, *65*, 9125. (d) Takasu, M.; Yamamoto, H. *Synlett* **1990**, 194. (e) Sartor, D.; Saffrich, J.; Helmchen, G. *Synlett* **1990**, 197. (f) Corey, E. J.; Guzman-Perez, A.; Loh, T.-P. *J. Am. Chem. Soc.* **1994**, *116*, 3611. (g) Pan, J.-F.; Chen, K. *J. Mol. Catal. A: Chem.* **2001**, *176*, 19. (h) Yang, K.-S.; Chen, K. *Org. Lett.* **2002**, *4*, 1107.

10.1021/jo026318m CCC: $25.00
Published on Web 12/28/2002

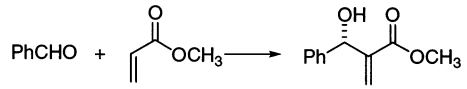
presence of acetic acid on a large scale. Treatment of racemic *trans*-1,2-diaminocyclohexane with (+)-ketopinic acid in refluxing $CHCl_3$ for 36 h provides **2** (31%) and **3** (45%), respectively. These two diastereomeric ligands can be separated by flash column chromatography, and the absolute stereochemistry of **3** was further confirmed by single-crystal X-ray analysis.

The lanthanide metal triflates were screened with the newly synthesized chiral ligands **1**−**4** using benzaldehyde and methyl acrylate (**A**) as model probes.[5] The catalytic system used in this study has a number of appealing features: (i) the molar ratio of chiral ligand to metal salts was designated to be 2:1 so that optimum enantioselectivity could be obtained under such conditions (deviation in either direction led to a decrease in selectivity, data not shown); (ii) a catalytic amount of catalyst (3 mol % of metal) is sufficient for asymmetric induction; (iii) the complexes are completely soluble in CH_3CN, giving a homogeneous solution in that ratio; and (iv) to prevent the formation of potential amine−Lewis acid complexes and therefore weaken the nucleophilic ability, a strictly controlled amount of DABCO (10 equiv to the catalyst or 30 mol % to substrate) was used. The use of chiral ligand **1** (6 mol %) with $Eu(OTf)_3$ (3 mol %) provided the Baylis−Hillman adduct with no asymmetric induction, while the use of $Yb(OTf)_3$ resulted in 17% ee (entries 1 and 2). The enantioselectivity was significantly improved when $La(OTf)_3$ was used (entry 3). The $La(OTf)_3$ catalyzed Baylis−Hillman reaction was next studied using other chiral ligands. The use of (*S*,*S*)-cyclohexyldiimino ligand **2** provided the desired Baylis−Hillman adduct with 67% ee, while the use of its diastereomeric ligand **3** provided the desired product with only 11% ee (entries 4 and 5). Diimine ligand **4** gave only polymerization products (entry 6). The use of **1**·$La(OTf)_3$ complexes appears to be the best combination for the reaction and was studied in great detail.

To further determine the feasibility of the catalytic system, a range of activated alkenes with suitable aldehydes were studied under optimized conditions. A variety of acrylates with diverse steric, geometric, and electronic properties were surveyed in this transformation. These included *tert*-butyl acrylate (**B**), phenyl acrylate (**C**), benzyl acrylate (**D**), and α-naphthyl acrylate (**E**).[9] The levels of asymmetric induction diminished appreciably when aliphatic aldehydes were treated with methylacrylate under the catalytic conditions employed (Table 2, entries 1−3). Good selectivity was obtained with low chemical yield when *tert*-butyl acrylate was used with benzaldehyde (entry 5). Excellent chemical yield with moderate stereoselectivity was obtained when phenyl acrylate (**C**) was treated with benzaldehyde (entry 6).

The stereoselectivity was remarkably enhanced when benzyl acrylate (**D**) was reacted with various aldehydes. A significant improvement in stereoselectivity was obtained when aliphatic aldehydes were reacted with benzyl acrylate (compare entry 1 with entry 2 and entry 7 with entry 8). The use of aromatic aldehydes with either electron-donating or -deficient substituents on the benzene ring gave high stereoselectivity (entries 10 and 11).

TABLE 1. Reaction of Benzaldehyde and Methyl Acrylate[a]

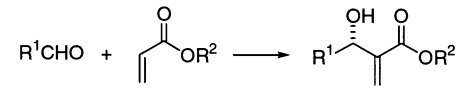


A **5**

entry	ligand	Lewis acid	yield (%)[b]	% ee[c]	configuration[d]
1	**1**	$Eu(OTf)_3$	81	0	*S*
2	**1**	$Yb(OTf)_3$	72	17	*S*
3	**1**	$La(OTf)_3$	75	84	*S*
4	**2**	$La(OTf)_3$	70	67	*S*
5	**3**	$La(OTf)_3$	71	11	*S*
6	**4**	$La(OTf)_3$	0		

[a] Benzaldehyde (0.5 mmol) was reacted with methyl acrylate **A** (0.5 mmol) in the presence of DABCO (30 mol %) and Lewis acid catalyst (3 mol %) in CH_3CN (2.6 mL) at room temperature for 10 h. [b] Isolated yield. [c] Determined by HPLC analysis using a chiral column. [d] Determined by comparison of optical rotation with the literature value.[8]

TABLE 2. Reaction of Acrylates A−E with Various Aldehydes Catalyzed by 1·La(OTf)$_3$ Complexes[a]



5

A $R^2 = CH_3$
B R^2 = t-Bu
C R^2 = Ph
D R^2 = Bn
E R^2 = α-Naphthyl

				5		
entry	acrylate	R^1CHO (R^1=)	*t* (h)	yield (%)[b]	configuration	(% ee)[c]
1	**A**	CH_3	10	85	*S*	10
2	**A**	CH_3CH_2	10	89	*S*	7
3	**A**	$(CH_3)_2CH$	10	75	*S*	6
4	**A**	4-$MeOC_6H_4$	10	55	*S*	66
5	**B**	Ph	10	25	*S*	70
6	**C**	Ph	10	97	*S*[d]	75
7	**D**	CH_3	10	85	*S*	65
8	**D**	CH_3CH_2	10	85	*S*	65
9	**D**	Ph	10	75	*S*[d]	75
10	**D**	4-$MeOC_6H_4$	10	50	*S*	95
11	**D**	4-$NO_2C_6H_4$	10	93	*S*	85
12	**E**	c-C_6H_{11}	1/3	71	*S*	71[e]
13	**E**	CH_3CH_2	1/3	75	*S*	70[f]
14	**E**	Ph	1/3	88	*S*[d]	81
15	**E**	4-$MeOC_6H_4$	1/3	35	*S*	95
16	**E**	4-$NO_2C_6H_4$	1/3	82	*S*	93
17	**E**	$Ph(CH_2)_2CH_2$	1/3	78	*S*	81

[a] All reactions were carried out at room temperature. [b] Isolated yield. [c] Determined by HPLC analysis using a chiral column. [d] Absolute stereochemistry was determined by HPLC analysis after conversion to known product **5A** (R^1 = Ph, R^2 = CH_3).[8] Absolute stereochemistry of other products was assigned by analogy. [e] % ee was determined by conversion to the corresponding ester **5A** (R^1 = c-C_6H_{11}, R^2 = CH_3) for HPLC analysis. [f] % ee was determined by conversion to the corresponding ester **5A** (R^1 = CH_3CH_2, R^2 = CH_3) for HPLC analysis.

The use of benzylacrylate to provide good to high levels of stereoselectivity in the Baylis−Hillman products is interesting. However, the reaction requires 10 h at room temperature for completion. The mechanism of the Baylis−Hillman reaction has been proposed, and the addition

(8) Drewes, S. E.; Emslie, N. D.; Field, J. S.; Kahn, A. A.; Ramesar, N. *Tetrahedron: Asymmetry* **1992**, *3*, 255.
(9) Lee, W.-D.; Yang, K.-S.; Chen, K. *Chem. Commun.* **2001**, 1612.

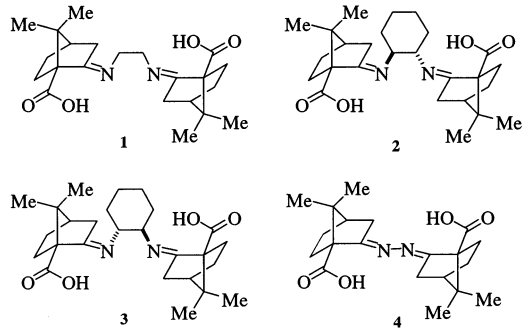


FIGURE 1. Structures of camphor-derived chiral ligands **1**−**4**.

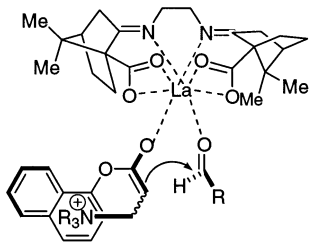


FIGURE 2. Proposed mechanism of the enantioselective Baylis−Hillman reaction.

of ammoniumenolate to an aldehyde was thought to be the rate-determining step.[5a] Stabilization of the enolate species would enhance the addition of DABCO to the acrylate and therefore accelerate the reaction rates. On the basis of this rationale and the results obtained above, the larger steric volume of aromatic acrylate should proceed at a higher reaction rate. To test this hypothesis, α-naphthyl acrylate (**E**) was prepared and subjected to the reaction conditions. To this end, treatment of the cyclohexanecarboxaldehyde with α-naphthyl acrylate afforded the desired product in 71% yield in *20 min* (entry 12). The enantioselectivity was determined to be 71% ee. In the case of aromatic aldehydes, high levels of stereoselectivities were obtained under the same reaction conditions (entries 14−16). Although a detailed understanding of the mechanism of this reaction remained unclear, the enantiofacial bias may be rationalized as follows. The hexadentate ligand binds to the metal atom, followed by the coordination of the azaenolate and aldehyde from the less hindered bottom side (Figure 2).[5a,10] The azaenolate attacks the *re* face of the aldehyde carbonyl sp^2 carbon center leading to the desired (*S*)-hydroxy configuration. The remarkable rate acceleration can be attributed to the potential π-charge stabilization of the intermediates between the naphthalene aromatic system with the azaenolate.[9] The same stereocontrol elements of the catalyst are still operative for α-naphthyl acrylate.

In conclusion, an effective chiral Lewis acid-catalyzed asymmetric Baylis−Hillman reaction has been described. Good to high enantioselectivities can be obtained using 3 mol % catalyst. *In addition, when α-naphthyl acrylate is used as a Michael acceptor, the reaction is complete within 20 min, in reasonable chemical yields. This represents the first practical demonstration that asymmetric induction can be obtained by the aid of a chiral Lewis acid.* Studies of the origin of the rate acceleration, as well as the stereochemical bias, are currently in progress in our laboratory.

(10) Hahn, F. E.; Mohr, J. *Chem. Ber.* 1**990**, *123*, 481.

Experimental Section

General Methods. All reactions were carried out in flame- or oven-dried glassware under a positive pressure of nitrogen. Air- and moisture-sensitive compounds were introduced by the use of a cannula through a rubber septum. Most reagents were commercially available and of synthetic grade. Tetrahydrofuran was distilled from sodium/benzophenone ketyl. Dichloromethane and toluene were dried over CaH_2 and distilled before use. Analytical thin-layer chromatography was performed using silica gel 60F glass plates, and flash column chromatography was performed using silica gel 60 (230−400 mesh). HRMS values were measured by either chemical ionization (MS-CI) or electronic impact (MS-EI). Elemental analyses were performed by Taipei Instrumentation Center, College of Science (National Taiwan University). ^{1}H and ^{13}C NMR spectra were recorded routinely in $CDCl_3$ on a 200 or 400 MHz instrument. Enantiomeric ratios were determined using a chiral column via HPLC analysis.

General Procedure for the Preparation of Diimino Chiral Ligands 1−4. To a solution of (+)-ketopinic acid (10 g, 54.9 mmol) in $CHCl_3$ (100 mL) were added ethylenediamine (1.64 g, 27.4 mmol) and acetic acid (0.1 mL) at room temperature. The resulting mixture was refluxed for 36 h and the reaction then quenched with H_2O (50 mL). The resulting solution was extracted with CH_2Cl_2 (100 mL), and the layers were separated. The organic layer was washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by silica gel using 4/1 EtOAc/CH_2Cl_2 as the eluent to give 7.22 g (69%) of chiral ligand **1** as a white solid: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.65 (dd, J = 15.0, 3.8 Hz, 4H), 2.56 (dd, J = 18.2, 3.6 Hz, 2H), 2.40 (td, J = 12.2, 3.6 Hz, 2H), 2.15−1.97 (m, 6H), 1.68 (td, J = 12.8, 4.0 Hz, 2H), 1.43−1.30 (m, 2H,), 1.25 (s, 6H), 0.87 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 185.09, 173.21, 60.68, 50.78, 50.30, 43.86, 35.40, 31.62, 27.84, 20.07, 19.85; MS *m*/*z* (rel intensity) 388 (M^+, 8), 373 (10), 319 (100), 163 (23), 148 (30); HRMS *m*/*z* 388.2336 (calcd for $C_{22}H_{32}N_2O_4$ 388.2362).

2: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.45 (m, 2H), 2.52 (m, 2H), 2.36 (m, 2H), 2.11−1.98 (m, 6H), 1.81−1.67 (m, 4H,), 1.60−1.24 (m, 6H), 1.22 (s, 6H), 0.86(s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 183.34, 173.13, 64.38, 60.19, 50.37, 43.68, 34.99, 31.77, 30.54, 27.84, 23.76, 20.04, 19.57; HRMS *m*/*z* 442.2834 (calcd for $C_{26}H_{38}N_2O_4$ 442.2832).

3: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.43 (dd, J = 5.2, 3.2 Hz, 2H), 2.61 (t, J = 3.0 Hz, 1H), 2.54 (t, J = 3.8 Hz, 1H), 2.35 (td, J = 12.1, 4.6 Hz, 2H), 2.11−1.92 (m, 6H), 1.83 (d, J = 6.6 Hz, 2H), 1.65−1.27 (m, 10H), 1.25−1.24 (m, 2H), 1.23 (s, 6H), 0.83 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 183.24, 173.10, 64.33, 60.55, 49.31, 43.93, 34.93, 32.41, 31.07, 27.90, 23.85, 20.17, 20.06; MS *m*/*z* (rel intensity) 442 (M^+, 7), 262 (35), 217 (50), 148 (45), 81 (100); HRMS *m*/*z* 442.2833 (calcd for $C_{26}H_{38}N_2O_4$ 442.2832). Crystal data for **3** at 22 °C: $C_{26}H_{38}N_2O_4$, M = 442.59, tetragonal, $P4_32_12$, a = 7.8028(13) Å, c = 40.282(4) Å, V = 2452.5 Å^3, Z = 4, λ = 0.70930 Å, F(000) = 960.56, D_c = 1.199 Mg/m^3, μ = 0.08 mm^{-1}, 5242 reflections, 146 parameters, R = 0.051, R_w = 0.067 for all data.

4: Dichloromethane was used as a solvent for this reaction. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.86 (t, J = 3.6 Hz, 1H), 2.74 (t, J = 3.8 Hz, 1H), 2.53 (td, J = 12.6, 4.8 Hz, 2H), 2.32−2.04 (m, 6H), 1.82 (td, J = 9.0, 4.2 Hz, 2H), 1,45 (m, 2H), 1.29 (s, 6H), 0.98 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 181.90, 171.84, 60.99, 51.74, 44.03, 35.63, 31.65, 27.69, 20.01, 19.89; MS *m*/*z* (rel intensity) 360 (M^+, 10), 316 (40), 288 (60), 163 (75), 148 (100), 134 (80), 95 (90); HRMS *m*/*z* 360.2011 (calcd for $C_{20}H_{28}N_2O_4$ 360.2049). Crystal data for **4** at 22 °C: $C_{20}H_{28}N_2O_4$, M = 360.45, monoclinic, $C2$, a = 11.414(3) Å, b = 7.580(4) Å, c = 21.887(3) Å, V = 1865.4 Å^3, Z = 4, λ = 0.70930 Å, F(000) =

776.48, $D_c = 1.283$ Mg/m^3, $\mu = 0.09$ mm^{-1}, 1812 reflections, 235 parameters, $R = 0.042$, $R_w = 0.079$ for all data.

General Procedure for the Asymmetric Baylis−Hillman Reaction. To a solution of chiral ligand **1** (12 mg, 0.03 mmol) in CH_3CN (2.6 mL) was added La(OTf)$_3$ (9 mg, 0.015 mmol) at room temperature under an N_2 atmosphere. This was stirred for 10 min, and benzaldehyde (54 mg, 0.51 mmol), α-naphthyl acrylate (0.10 g, 0.51 mmol), and DABCO (17 mg, 0.15 mmol) were added sequentially. The resulting mixture was stirred for 20 min and the reaction quenched with H_2O (5 mL). The mixture was extracted with CH_2Cl_2 (10 mL), and the layers were separated. The organic layer was washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by silica gel using 8/1 hexane/EtOAc as an eluent to give 0.13 g (88%) of **5E** (R^1= Ph) as a white solid. The enantiomeric ratios were determined by HPLC analyses using a chiral column.

Methyl (*S*)-3-Hydroxy-3-phenyl-2-methylenepropanoate. Colorless oil (84% ee): $[\alpha]_D = +93.3°$ (c 1.0, $CHCl_3$); lit.[8] $[\alpha]_D = -111.1°$ (*c* 1.11, MeOH) for the (*R*)-enantiomer. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.38−7.26 (m, 5H), 6.32 (d, $J = 1.2$ Hz, 1H), 5.85 (d, $J = 1.2$ Hz, 1H), 5.54 (s, 1H), 3.69 (1, 3H), 3.13 (br, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.71, 142.06, 141.32, 128.33, 127.72, 126.57, 125.85, 72.89, 51.72; MS *m*/*z* (rel intensity) 192 (M^+, 20), 191 (30), 160 (45), 105 (100), 77 (40); HRMS *m*/*z* 192.0777 (calcd for $C_{11}H_{12}O_3$ 192.0786). HPLC condition: 20/80 2-propanol/hexane (0.5 mL/min), $t_R = 13.3$ min (*S*) and 15.3 min (*R*).

Methyl (*S*)-3-Hydroxy-2-methylenebutanoate. Colorless oil (10% ee): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.11 (d, $J = 1.0$ Hz, 1H), 5.76 (d, $J = 1.0$ Hz, 1H), 4.54 (q, $J = 6.4$ Hz, 1H), 3.67 (s, 3H), 3.16 (br, 1H), 1.38 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.94, 143.73, 123.84, 66.46, 51.59, 22.03; MS *m*/*z* (rel intensity) 129 (M^+, 5), 115 (65), 87 (80), 83 (100), 55 (55). HPLC condition: 2/98 2-propanol/hexane (0.8 mL/min), $t_R = 17.3$ min (*R*) and 19.4 min (*S*).

Methyl (*S*)-3-Hydroxy-2-methylenepentanoate. Colorless oil (7% ee): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.15 (d, $J = 1.0$ Hz, 1H), 5.74 (d, $J = 1.0$ Hz, 1H), 4.27 (t, $J = 6.2$ Hz, 1H), 3.69 (s, 3H), 2.91 (br, 1H), 1.68−1.46 (qd, $J = 7.4$, 6.2 Hz, 2H), 0.86 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.97, 142.41, 124.75, 72.16, 51.54, 28.86, 9.65. HPLC condition: 2/98 2-propanol/hexane (0.5 mL/min), $t_R = 20.7$ min (*R*) and 23.2 min (*S*).

Methyl (*S*)-3-Hydroxy-3-(*p*-methoxyphenyl)-2-methylenepropanoate. White solid (66% ee): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.28 (dd, $J = 9.0$, 2.2 Hz, 2H), 6.86 (dd, $J = 9.0$, 2.2 Hz, 2H), 6.29 (d, $J = 1.0$ Hz, 1H), 5.85 (d, $J = 1.2$ Hz, 1H), 5.49 (d, $J = 4.8$ Hz, 1H), 3.76 (s, 3H), 3.68 (s, 3H), 3.14 (d, $J = 5.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.73, 159.17, 142.26, 133.52, 127.89 (×2), 125.32, 113.72 (×2), 72.43, 55.06, 51.71; MS *m*/*z* (rel intensity) 222 (M^+, 10), 143 (100), 115 (40), 105 (35), 91 (60), 83 (30); HRMS *m*/*z* 222.0887 (calcd for $C_{12}H_{14}O_4$ 222.0892). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.80; H, 6.34. HPLC condition: 20/80 2-propanol/hexane (0.7 mL/min), $t_R = 11.2$ min (*S*) and 14.1 min (*R*).

Methyl (*S*)-3-Hydroxy-3-(*p*-nitrophenyl)-2-methylenepropanoate. White solid (17% ee): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.16 (d, $J = 8.8$ Hz, 2H), 7.55 (d, $J = 8.8$ Hz, 2H), 6.37 (d, $J = 1.0$ Hz, 1H), 5.88 (d, $J = 1.0$ Hz, 1H), 5.61 (s, 1H), 3.71 (s, 3H), 3.12 (br, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.43, 148.72, 147.48, 141.09, 127.37, 127.16, 123.58, 72.51, 52.09; MS *m*/*z* (rel intensity) 237 (M^+, 20), 220 (50), 205 (40), 177 (100), 150 (85), 115 (20), 77 (20), 55 (20). HRMS *m*/*z* 237.0637 (calcd for $C_{11}H_{11}NO_5$ 237.0637). HPLC condition: 20/80 2-propanol/hexane (0.7 mL/min), $t_R = 12.7$ min (*S*) and 13.8 min (*R*).

***tert*-Butyl (*S*)-3-Hydroxy-3-phenyl-2-methylenepropanoate.** White solid (70% ee): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.35−7.25 (m, 5H), 6.24 (d, $J = 1.0$ Hz, 1H), 5.75 (d, $J = 1.0$ Hz, 1H), 5.47 (s, 1H), 3.37 (br, 1H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.61, 143.52, 141.66, 128.22 (×2), 127.55, 126.57 (×2), 124.93, 81.40, 73.15, 27.72 (x3). HPLC condition: 10/90 2-propanol/hexane (0.5 mL/min), $t_R = 8.1$ min (*S*) and 10.4 min (*R*).

Phenyl (*S*)-3-Hydroxy-3-phenyl-2-methylenepropanoate. Colorless oil (75% ee): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.49−7.21 (m, 8H), 7.05−7.00 (m, 2H), 6.62 (d, $J = 1.0$ Hz, 1H), 6.11 (d, $J = 1.0$ Hz, 1H), 5.68 (s, 1H), 3.01 (br, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 164.70, 150.34, 141.89, 141.19, 129.34 (×2), 128.45 (×2), 127.92, 127.21 (×2), 126.72, 125.89, 121.39 (×2), 72.77; MS *m*/*z* (rel intensity) 254 (M^+, 5), 161 (100), 133 (45), 117 (95), 94 (95), 77 (45). HRMS *m*/*z* 254.0921 (calcd for $C_{16}H_{14}O_3$ 254.0943). HPLC condition: 20/80 2-propanol/hexane (0.5 mL/min), $t_R = 15.5$ min (*R*) and 19.5 min (*S*).

Benzyl (*S*)-3-Hydroxy-2-methylenebutanoate. Colorless oil (65% ee): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.39−7.26 (m, 5H), 6.27 (s, 1H), 5.86 (s, 1H), 5.22 (s, 2H), 4.65 (q, $J = 6.4$ Hz, 1H), 2.77 (br, 1H), 1.38 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.43, 143.61, 135.66, 128.60 (×2), 128.31, 128.09 (×2), 124.41, 66.88, 66.47, 22.00; MS *m*/*z* (rel intensity) 206 (M^+, 5), 143 (15), 107 (20), 91 (95), 82 (100), 54 (55). HRMS *m*/*z* 206.0917 (calcd for $C_{12}H_{14}O_3$ 206.0943). HPLC condition: 2/98 2-propanol/hexane (0.5 mL/min), $t_R = 25.0$ min (*R*) and 27.6 min (*S*).

Benzyl (*S*)-3-Hydroxy-2-methylenepentanoate. Colorless oil (65% ee): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.37−7.29 (m, 5H), 6.27 (d, $J = 1.0$ Hz, 1H), 5.84 (d, $J = 1.0$ Hz, 1H), 5.19 (s, 2H), 4.40 (t, $J = 6.2$ Hz, 1H), 3.19 (s, 1H), 1.67 (qd, $J = 7.4$, 6.2 Hz, 2H), 0.93 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.36, 142.30, 135.66, 128.56 (×2), 128.25, 128.02 (×2), 125.29, 72.66, 66.40, 28.97, 9.88; MS *m*/*z* (rel intensity) 220 (M^+, 5), 181 (10), 173 (10), 96 (55), 91 (100), 68 (20). HRMS *m*/*z* 220.1088 (calcd for $C_{13}H_{16}O_3$ 220.1099). HPLC condition: 2/98 2-propanol/hexane (0.8 mL/min), $t_R = 23.7$ min (*R*) and 26.1 min (*S*).

Benzyl (*S*)-3-Hydroxy-3-phenyl-2-methylenepropanoate. Colorless oil (75% ee): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.39−7.23 (m, 10H), 6.42 (s, 1H), 5.91 (d, $J = 1.0$ Hz, 1H), 5.59 (s, 1H), 5.15 (s, 2H), 2.95 (br, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.06, 142.07, 141.32, 135.50, 128.49 (×2), 128.40 (×2), 128.21, 128.01 (×2), 127.80, 126.67, 126.22, 73.00, 66.50; MS *m*/*z* (rel intensity) 268 (M^+, 2), 177 (100), 162 (10), 159 (20), 105 (10), 91 (10). HPLC condition: 20/80 2-propanol/hexane (0.5 mL/min), $t_R = 15.1$ min (*S*) and 16.1 min (*R*).

Benzyl (*S*)-3-Hydroxy-3-(*p*-methoxyphenyl)-2-methylenepropanoate. White solid (95% ee): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.43−7.21 (m, 7H), 6.90−6.83 (m, 2H), 6.39 (d, $J = 1.0$ Hz, 1H), 5.90 (d, $J = 1.0$ Hz, 1H), 5.55 (s, 1H), 5.14 (s, 2H), 3.80 (s, 3H), 2.70 (br, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.15, 159.31, 142.32, 135.60, 133.52, 128.51 (×2), 128.22 (×2), 128.01 (×2), 125.76 (×2), 113.84 (×2), 72.62, 66.47, 55.15; MS *m*/*z* (rel intensity) 298 (M^+, 5), 207 (85), 189 (75), 135 (100), 121 (35), 99 (20), 91 (80). HRMS *m*/*z* 298.1155 (calcd for $C_{18}H_{18}O_4$ 298.1205). HPLC condition: 20/80 2-propanol/hexane (0.7 mL/min), $t_R = 13.5$ min (*S*) and 16.5 min (*R*).

Benzyl (*S*)-3-Hydroxy-3-(*p*-nitrophenyl)-2-methylenepropanoate. White solid (85% ee): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.12 (d, $J = 8.6$ Hz, 2H), 7.51 (d, $J = 8.6$ Hz, 2H), 7.34−7.22 (m, 5H), 6.44 (s, 1H), 5.94 (d, $J = 1.0$ Hz, 1H), 5.63 (s, 1H), 5.13 (s, 2H), 3.32 (br, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.61, 148.67, 147.31, 141.16, 135.11, 128.51 (×2), 128.40, 128.10 (×2), 127.37 (×2), 127.22, 123.46 (×2), 72.22, 66.77; MS *m*/*z* (rel intensity) 313 (M^+, 3), 222 (15), 204 (35), 189 (85), 161 (80), 150 (25), 91 (100), 77 (15), 65 (15). HRMS *m*/*z* 313.0961 (calcd for $C_{17}H_{15}NO_5$ 313.0950). Anal. Calcd for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.83; N, 4.47. Found: C, 64.95; H, 4.70; N, 4.47. HPLC condition: 20/80 2-propanol/hexane (0.7 mL/min), $t_R = 16.8$ min (*S*) and 19.0 min (*R*).

α-Naphthyl (*S*)-3-Cyclohexyl-3-hydroxy-2-methylenepropanoate. Colorless oil (71% ee): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.92−7.76 (m, 3H), 7.57−7.46 (m, 3H), 7.28 (d, $J = 9.2$ Hz, 1H), 6.73 (d, $J = 1.0$ Hz, 1H), 6.05 (d, $J = 1.0$ Hz, 1H),

4.27 (d, J = 7.0 Hz, 1H), 2.30 (br, 1H), 2.07−2.00 (m, 1H), 1.84−1.67 (m, 5H), 1.33−1.02 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.29, 146.40, 140.84, 134.73, 128.16, 128.04, 126.66, 126.57, 126.26, 125.43, 121.03 (×2), 118.19, 77.18, 45.47, 30.04, 28.22, 26.28, 26.05, 25.86; MS m/z (rel intensity) 310 (M^+, 2), 144 (100), 115 (20), 83 (10), 55 (15). HRMS m/z 310.1575 (calcd for $C_{20}H_{22}O_3$ 310.1569). HPLC condition for methyl (*S*)-3-hydroxy-3-cyclohexyl-2-methylenepropanoate: 2/98 2-propanol/hexane (0.5 mL/min), t_R = 20.4 min (*R*) and 22.5 min (*S*).

α-Naphthyl (*S*)-3-Hydroxy-2-methylenepentanoate. Colorless oil (70% ee): $[\alpha]_D$ = +97.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.92−7.76 (m, 3H), 7.55−7.45 (m, 3H), 7.30 (dd, J = 7.6, 1.2 Hz, 1H), 6.71 (d, J = 1.0 Hz, 1H), 6.12 (d, J = 1.0 Hz, 1H), 4.54 (q, J = 6.4 Hz, 1H), 2.45 (br, 1H), 1.85 (qd, J = 7.4, 6.4 Hz, 2H), 1.05 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.15, 146.41, 141.97, 134.70, 128.12, 126.95, 126.84, 126.63, 126.54, 126.22, 125.38, 121.03, 118.15, 72.80, 29.12, 10.02; MS m/z (rel intensity) 256 (M^+, 3), 227 (5), 144 (100), 115 (10), 95 (5), 83 (5), 55 (10). HRMS m/z 256.1050 (calcd for $C_{16}H_{16}O_3$ 256.1099). HPLC condition for methyl (*S*)-3-hydroxy-2-methylenepentanoate: 2/98 2-propanol/hexane (0.5 mL/min), t_R = 20.7 min (*R*) and 23.2 min (*S*).

α-Naphthyl (*S*)-3-Hydroxy-3-phenyl-2-methylenepropanoate. White solid (81% ee): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.86 (d, J = 8.0 Hz, 1H) 7.80 (d, J = 8.0 Hz, 1H), 7.58−7.35 (m, 9H), 7.20 (dd, J = 7.6, 0.6 Hz, 1H), 6.78 (d, J = 1.0 Hz, 1H), 6.22 (d, J = 1.0 Hz, 1H), 5.78 (s, 1H), 3.15 (br, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 164.94, 146.31, 141.77, 141.15, 134.62, 128.71 (×2), 128.18, 127.99, 127.60, 126.90 (×2), 126.69, 126.52, 126.48, 126.26, 125.32, 121.05, 118.06, 73.21; MS m/z (rel intensity) 304 (M^+, 5), 286 (3), 161 (5), 144 (100), 115 (75), 105 (10), 77 (15), 55 (5). HRMS m/z 304.1144 (calcd for $C_{20}H_{16}O_3$ 304.1099). Anal. Calcd for $C_{20}H_{16}O_3$: C, 78.93; H, 5.30. Found: C, 78.82; H, 5.20. HPLC condition: 20/80 2-propanol/hexane (0.6 mL/min), t_R = 25.4 min (*S*) and 29.1 min (*R*).

α-Naphthyl (*S*)-3-Hydroxy-3-(*p*-methoxyphenyl)-2-methylenepropanoate. White solid (95% ee): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.83 (d, J = 7.4 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.52−7.35 (m, 6H), 7.16 (dd, J = 7.4, 0.8 Hz, 1H), 6.93 (dd, J = 8.8, 2.2 Hz, 2H), 6.76 (d, J = 1.0 Hz, 1H), 6.20 (d, J = 1.0 Hz, 1H), 5.75 (s, 1H), 3.83 (s, 3H), 2.82 (br, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 164.98, 159.61, 146.38, 142.65, 133.38, 128.28 (×2), 127.99, 127.07, 126.73, 126.48 (×2), 126.23, 125.35, 121.12, 118.09, 114.10 (×2), 72.75, 55.29; MS m/z (rel intensity) 318 (M^+, 20), 272 (30), 191 (100), 163 (20), 144 (90), 115 (60), 77 (10). HRMS m/z 318.1230 (calcd for $C_{21}H_{18}O_3$ 318.1256). HPLC condition: 10/90 2-propanol/hexane (0.8 mL/min), t_R = 21.3 min (*S*) and 25.9 min (*R*).

α-Naphthyl (*S*)-3-Hydroxy-3-(*p*-nitrophenyl)-2-methylenepropanoate. White solid (93% ee): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.86 (dd, J = 9.0, 2.0 Hz, 2H), 7.86 (d, J = 8.8 Hz, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.56−7.43 (m, 6H), 7.16 (dd, J = 7.6, 1.0 Hz, 1H), 6.83 (d, J = 1.0 Hz, 1H), 6.20 (d, J = 1.0 Hz, 1H), 5.80 (s, 1H), 3.30 (br, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 164.57, 148.43, 147.54, 146.05, 140.89, 134.61, 128.65, 128.12, 127.55, 126.60, 126.43, 125.31, 123.69, 120.67, 117.98, 72.24; MS m/z (rel intensity) 349 (M^+, 3), 189 (3), 176 (5), 160 (5), 144 (100), 115 (30), 77 (5), 55 (5). HRMS m/z 349.0951 (calcd for $C_{20}H_{15}NO_5$ 349.0950). HPLC condition: 20/80 2-propanol/hexane (0.8 mL/min), t_R = 22.2 min (*S*) and 31.9 min (*R*).

α-Naphthyl (*S*)-3-Hydroxy-5-phenyl-2-methylenepentanoate. Colorless oil (81% ee): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.93−7.77 (m, 3H), 7.58−7.46 (m, 3H), 7.36−7.18 (m, 6H), 6.73 (d, J = 1.0 Hz, 1H), 6.15 (d, J = 1.0 Hz, 1H), 4.63 (dd, J = 7.6, 4.8 Hz, 1H), 3.01−2.75 (m, 2H), 2.72 (br, 1H), 2.21−2.07 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.15, 146.38, 142.09, 141.56, 134.72, 128.54, 128.51, 128.15, 127.05, 126.83, 126.67, 126.58, 126.29, 126.01, 125.41, 121.03, 118.16, 70.90, 37.70, 32.05; MS m/z (rel intensity) 332 (M^+, 3), 227 (5), 171 (10), 144 (100), 115 (55), 91 (90), 77 (5), 65 (5), 55 (5). HRMS m/z 332.1389 (calcd for $C_{22}H_{20}O_3$ 332.1412). HPLC condition: 10/90 2-propanol/hexane (0.6 mL/min), t_R = 41.5 min (*R*) and 53.7 min (*S*).

Acknowledgment. This work is supported by the National Science Council of the Republic of China and the National Taiwan Normal University (ORD 91-2). The X-ray crystal data, collected and processed by Taipei Instrumentation Center, College of Science (National Taiwan University), and Professor C.-H. Ueng (National Taiwan Normal University), are gratefully acknowledged.

Supporting Information Available: Spectroscopic data (^{1}H and ^{13}C NMR) for all new compounds and crystallographic information including experimental details, bond lengths, bond angles, and ORTEP diagrams for ligands **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026318M