Highly Efficient Asymmetric Synthesis of β-Amino Acid Derivatives via Rhodium-Catalyzed Hydrogenation of β-(Acylamino)acrylates

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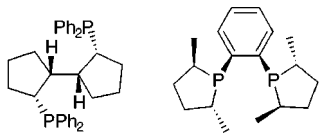
Received March 30, 1999

Enantiomerically pure β-amino acids and their derivatives are important building blocks for the synthesis of β-peptides, β-lactam antibiotics, and many important drugs (e.g., taxol side chain).[1] Peptides containing β-amino acids show increased stability to enzymatic hydrolysis and are being evaluated as promising pharmaceutical products. Recent studies show that a variety of β-peptides can fold in a specific conformation, and these may lead design of molecules with unique properties.[2] For these reasons, enantioselective synthesis of β-amino acids has attracted extensive interest. Although several stoichiometric and catalytic methods have been developed to make chiral β-amino acids,[3] straightforward hydrogenation of 3-aminoacrylic acid derivatives represents one of the simplest and efficient routes. However, previous attempts at this asymmetric hydrogenation using Rh and Ru catalysts led to poor enantioselectivity.[4] Herein, we report the first highly enantioselective hydrogenation of β-(acylamino)acrylates for the synthesis of β-amino acid derivatives using Rh−BICP and Rh−DuPhos catalytic systems (Figure 1).

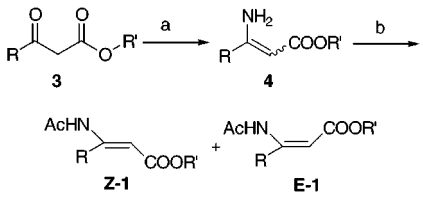
We have previously demonstrated that Rh−BICP complexes are highly enantioselective catalysts for hydrogenation of dehydroamino acids and *E*/*Z* mixtures of enamides.[5] Another catalytic system for hydrogenation of an isomeric mixture of (*Z*)- and (*E*)-enamides with high enantioselectivity is Burk's Rh−DuPhos catalyst.[6] Prompted by these results, we have applied this catalyst to hydrogenation of 3-aminoacrylic acid derivatives **1**. Substrates **1a**−**1h** can be conveniently made from the corresponding β-keto esters **3** to give 3-amino-2-alkenoates **4**, followed by acylation (Scheme 1).[4] The *E*/*Z* mixture of enamides (**1a**−**1g**) can be separated by column chromatography except for substrate **1h**. To search for the optimal conditions for the hydrogenation reaction, we have performed a number of experiments using methyl 3-acetamino-2-butenoate (**1a**) as a prototypical substrate (Table 1). Acylation of the parent β-amino crotonate with Ac_2O in THF gave a 1:1.6 mixture of (*E*)-**1a** and (*Z*)-**1a**, which can be separated on a silica gel column with EtOAc/hexanes as eluent. Unlike the results obtained with a Ru−BINAP catalyst in which (*Z*)-**1a** was hydrogenated faster than (*E*)-**1a** in a competitive experiment,[4a] (*E*)-**1a** is more reactive than (*Z*)-**1a** in the Ru−BICP-catalyzed hydrogenation. Under 40 psi of H_2, (*E*)-**1a** was completely reduced to (*R*)-**2a** in 24 h (entry 3), while (*Z*)-**1a** is not reactive under these conditions. Higher H_2 pressure (294 psi) is required for complete reduction of (*Z*)-**1a** (entry 14). Different catalyst precursors were also tested for hydrogenation of (*E*)-**1a**, and a cationic Rh(I) species gave better results than a neutral Rh(I) complex (entries 1−3). A change of H_2 pressure has no obvious effect on the enantioselectivity in the hydrogenation of (*E*)-**1a** (entries 3−5). A study of solvent effects indicates that toluene is a good solvent (entries 6−10 and entry 3), while the ee is significantly lower in MeOH (entry 10). Therefore, the optimal conditions for hydrogenation of (*E*)-**1a** using a Rh−BICP catalyst was as shown in entry 3. Under these experimental conditions, other bidentate chiral phosphines were tried for hydrogenation of (*E*)-**1a**. While hydrogenation of (*E*)-**1a** with Rh−DIOP (entry 11, 79.0% ee) and Rh−BINAP species (entry 12, 69.0% ee) gave lower ee's than the result with the Rh−BICP complex (entry 3, 96.1% ee), a slightly higher ee was obtained with a Rh−Me−DuPhos catalyst (entry 13,



(*R*, *R*)-BICP (*R*, *R*)-Me-DuPhos

Figure 1.

Scheme 1[a]



[a] Conditions: (a) NH_4OAc, MeOH, rt; (b) Ac_2O, py, THF, reflux.

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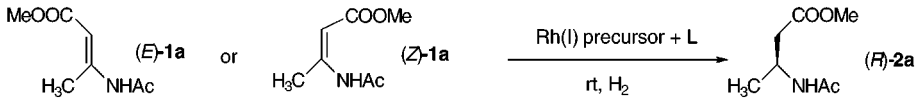
10.1021/jo990565h CCC: $18.00
Published on Web 08/10/1999

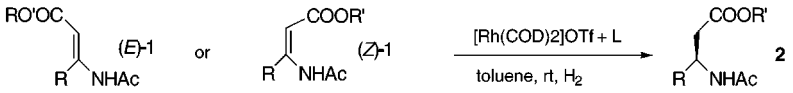
Table 1. Ligand Effect on Rh-Catalyzed Asymmetric Hydrogenation of an Enamide[a]



entry	ligand	substrate	Rh(I) precursor	solvent	H_2 pressure, psi	conv, %	% ee[b]
1	(*R*,*R*)-BICP	(*E*)-**1a**	$[Rh(COD)Cl]_2$	toluene	40	94.5	63.2
2	(*R*,*R*)-BICP	(*E*)-**1a**	$[Rh(COD)_2]BF_4$	toluene	40	100	95.1
3	(*R*,*R*)-BICP	(*E*)-**1a**	$[Rh(COD)_2]OTf$	toluene	40	100	96.1
4	(*R*,*R*)-BICP	(*E*)-**1a**	$[Rh(COD)_2]OTF$	toluene	14.7	82.8	94.9
5	(*R*,*R*)-BICP	(*E*)-**1a**	$[Rh(COD)_2]OTf$	toluene	735	100	95.9
6	(*R*,*R*)-BICP	(*E*)-**1a**	$[Rh(COD)_2]OTf$	hexanes	40	100	91.0
7	(*R*,*R*)-BICP	(*E*)-**1a**	$[Rh(COD)_2]OTf$	benzene	40	100	95.9
8	(*R*,*R*)-BICP	(*E*)-**1a**	$[Rh(COD)_2]OTf$	THF	40	100	94.4
9	(*R*,*R*)-BICP	(*E*)-**1a**	$[Rh(COD)_2]OTf$	CH_2Cl_2	40	100	93.5
10	(*R*,*R*)-BICP	(*E*)-**1a**	$[Rh(COD)_2]OTf$	MeOH	40	100	85.4
11	(+)-DIOP	(*E*)-**1a**	$[Rh(COD)_2]OTf$	toluene	40	100	79.0
12	(*R*)-BINAP	(*E*)-**1a**	$[Rh(COD)_2]OTf$	toluene	40	100	69.0
13	(*R*,*R*)-Me−DuPhos	(*E*)-**1a**	$[Rh(COD)_2]OTf$	toluene	40	100	99.3
14	(*R*,*R*)-BICP	(*Z*)-**1a**	$[Rh(COD)_2]OTf$	toluene	294	100	88.6
15	(*R*,*R*)-Me−DuPhos	(*Z*)-**1a**	$[Rh(COD)_2]OTf$	toluene	294	100	63.7

[a] The reaction was conducted at rt under H_2 for 24 h. The catalyst was made in situ by stirring a solution of Rh(I) precursor and ligand for 30 min {[substrate (0.5 mmol, 0.125 M):$[Rh(COD)_2]OTf$:ligand = 1:0.01:0.011]}. [b] Enantiomeric excesses were determined by GC using a CHIRAL SELECT 1000 column.

Table 2. Rh-Catalyzed Asymmetric Hydrogenation of Enamide for the Synthesis of *β*-Amino Acid Derivatives[a]



entry	ligand	substrate	R	R′	H_2 pressure, psi	% ee[b]	conv, %
1	(*R*,*R*)-BICP	(*E*)-**1b**	Et	Me	40	96.8 (*R*)	100
2	(*R*,*R*)-Me−DuPhos	(*E*)-**1b**	Et	Me	40	99.6 (*R*)	100
3	(*R*,*R*)-BICP	(*Z*)-**1b**	Et	Me	294	86.9 (*R*)	100
4	(*R*,*R*)-Me−DuPhos	(*Z*)-**1b**	Et	Me	294	21.2 (*R*)	100
5	(*R*,*R*)-BICP	(*E*)-**1c**	*i*-Bu	Me	40	90.9 (*R*)	100
6	(*R*,*R*)-Me−DuPhos	(*E*)-**1c**	*i*-Bu	Me	40	98.5 (*R*)	100
7	(*R*,*R*)-BICP	(*Z*)-**1c**	*i*-Bu	Me	294	92.9 (*R*)	93
8	(*R*,*R*)-Me−DuPhos	(*Z*)-**1c**	*i*-Bu	Me	294	62.4 (*R*)	96
9	(*R*,*R*)-BICP	(*E*)-**1d**	Me	Et	40	96.0 (*R*)	100
10	(*R*,*R*)-Me−DuPhos	(*E*)-**1d**	Me	Et	40	98.7 (*R*)	100
11	(*R*,*R*)-BICP	(*Z*)-**1d**	Me	Et	294	88.0 (*R*)	100
12	(*R*,*R*)-Me−DuPhos	(*Z*)-**1d**	Me	Et	294	62.3 (*R*)	100
13	(*R*,*R*)-BICP	(*E*)-**1e**	Pr	Et	40	96.6 (*R*)	100
14	(*R*,*R*)-Me−DuPhos	(*E*)-**1e**	Pr	Et	40	99.6 (*R*)	100
15	(*R*,*R*)-BICP	(*Z*)-**1e**	Pr	Et	294	90.7 (*R*)	100
16	(*R*,*R*)-Me−DuPhos	(*Z*)-**1e**	Pr	Et	294	34.4 (*R*)	100
17	(*R*,*R*)-BICP	(*E*)-**1f**	*i*-Pr	Et	40	97.0 (*S*)	100
18	(*R*,*R*)-Me−DuPhos	(*E*)-**1f**	*i*-Pr	Et	40	97.6 (*S*)	100
19	(*R*,*R*)-BICP	(*Z*)-**1f**	*i*-Pr	Et	294	91.0 (*S*)	100
20	(*R*,*R*)-Me−DuPhos	(*Z*)-**1f**	*i*-Pr	Et	294	42.1 (*S*)	100
21	(*R*,*R*)-BICP	(*E*)-**1g**	Me	*i*-Pr	40	95.6 (*R*)	100
22	(*R*,*R*)-Me−DuPhos	(*E*)-**1g**	Me	*i*-Pr	40	98.1 (*R*)	100
23	(*R*,*R*)-BICP	(*Z*)-**1g**	Me	*i*-Pr	294	86.4 (*R*)	100
24	(*R*,*R*)-Me−DuPhos	(*Z*)-**1g**	Me	*i*-Pr	294	61.9 (*R*)	100
25	(*R*,*R*)-BICP	(*E*/*Z*)-**1h**	Ph	Me	294	66.0 (*S*)	100
26	(*R*,*R*)-Me−DuPhos	(*E*/*Z*)-**1h**	Ph	Me	294	65.1 (*S*)	100

[a] The reaction was conducted at rt under H_2 for 24 h. The catalyst was made in situ by stirring a solution of $[Rh(COD)_2]OTf$ and ligand for 30 min {[substrate (0.5 mmol, 0.125 M):$[Rh(COD)_2]OTf$:ligand = 1:0.01:0.011]}. [b] Enantiomeric excesses were determined by GC using a CHIRAL SELECT 1000 column or *γ*-DEX-225.

99.3% ee). However, enantioselectivity in hydrogenation of (*Z*)-**1a** with the Rh−BICP catalyst (entry 14, 88.6% ee) is significantly higher than that achieved with the Rh−Me−DuPhos complex (entry 15, 63.7% ee).

On the basis of the hydrogenation conditions for (*E*)-**1a** and (*Z*)-**1a**, a variety of 3-aminoacrylic acid derivatives were reduced using Rh−BICP and Rh−Me−DuPhos catalysts (Table 2). In general, hydrogenation of an *E* isomer of enamides gave a higher ee than the corresponding *Z* isomer (an exception is with substrate **1a** and a Rh−BICP catalyst, entries 5 and 7), and hydrogenation of the *E* isomer is faster than with the corresponding *Z* isomer. Changing the ester groups and alkyl substituents of 3-aminoacrylic acid derivatives shows minor variations in both enantioselectivity and reactivity with both Rh−BICP and Rh−Me−DuPhos catalysts (entries 1−24).

Overall, Rh−Me−DuPhos is a slightly more enantioselective catalyst for hydrogenation of the *E* isomers of enamides **1b**−**1g** than is the Rh−BICP catalyst. On the other hand, Rh−BICP is a superior catalyst for hydrogenation of the *Z* isomers of **1b**−**1g** compared to the Rh−Me−DuPhos complex. For example, Rh−Me−DuPhos-catalyzed hydrogenation of (*Z*)-**1b** only gave 21.2% ee (entry 4) compared with 86.9% ee achieved with the Rh−

BICP catalyst (entry 3). From a practical point of view, hydrogenation of *E*/*Z* mixtures of β-(acylamino)acrylates with the Rh−BICP catalyst offers the most convenient access to corresponding β-amino acid derivatives because high enantiomeric excesses can be obtained from both isomers. Our results with Rh−BICP represent the highest enantioselectivity achieved for the hydrogenation of β-(acylamino)acrylates with alkyl substituents. A limitation of the reaction is that only moderate ee's were obtained with an aryl substituent in the β-(acylamino)-acrylates using both Rh−BICP and Rh−Me−DuPhos catalysts (entries 25 and 26).

In summary, highly enantioselective hydrogenation of the *E* isomer of β-(acylamino)acrylates with a Rh−Me−DuPhos catalyst and *E*/*Z* isomers of β-(acylamino)-acrylates with a Rh−BICP catalyst has been achieved in this study. This method provides an efficient approach to important β-amino acid building blocks. Future research will explore the scope of this reaction with other enamides, especially β-(acylamino)acrylates with an α-substituent or containing a ring.

Experimental Section

General Methods. All reactions and manipulations were performed in a nitrogen-filled glovebox or using standard Schlenk techniques. Toluene, benzene, and THF were distilled from sodium benzophenone ketyl under nitrogen. Methylene chloride was distilled from CaH_2. Methanol, ethanol, and 2-propanol were distilled from Mg under nitrogen. Chiral BICP ligand was prepared using previously described procedures.[5a] (*R*)-BINAP and (+)-DIOP were purchased from Aldrich. (*R*,*R*)-Me−DuPHOS was purchased from Strem. Column chromatography was performed using EM Merck Silica Gel 60 (230−400 mesh).

Synthesis of Substrates (Scheme 1): Step a. A solution of β-keto ester **3** (12 mmol) and NH_4OAc (4.6 g, 60 mmol) in MeOH (15 mL) was stirred at rt for 3 d. After the solvent was evaporated under reduced pressure, the residue was diluted with $CHCl_3$ (30 mL). The resulting solid was filtered off and washed with $CHCl_3$ (2 × 30 mL). The combined filtrate was washed with water and brine, and dried over sodium sulfate. Evaporation of the solvent gave the 3-amino-2-alkenoate **4**, which was used for the next step without purification.

Step b. To a solution of 3-amino-2-alkenoate **4** in THF (12 mL) were added pyridine (2 mL) and acetic anhydride (6 mL). The reaction mixture was then heated under reflux for 24 h. After the mixture was cooled to rt, the volatile was evaporated. The residue was dissolved in EtOAc (20 mL), and the solution was washed with water (10 mL), 1 N HCl (10 mL), 1 M KH_2PO_4 (10 mL), $NaHCO_3$ (saturated, 10 mL), and brine (15 mL). After the solution was dried over sodium sulfate, the solvent was evaporated under reduced pressure. Chromatography of the residue on silica gel with a gradient solvent of EtOAc in hexanes (15−70%) as eluant gave the *Z* isomer, followed by a byproduct and then the *E* isomer.

(*Z*)-Methyl 3-Acetamido-2-butenoate:[4a] ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.89 (s, 3 H), 2.24 (s, 3H), 3.57 (s, 3H), 4.76 (s, 1H), 10.9 (br, 1H).

(*E*)-Methyl 3-Acetamido-2-butenoate:[4a] ^{1}H NMR (360 MHz, acetone-d_6) δ 2.02 (s, 3 H), 2.29 (s, 3H), 3.58 (s, 3H), 6.85 (s, 1H), 8.72 (br, 1H).

(*Z*)-Ethyl 4-Methyl-3-acetamido-2-pentenoate:: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.10−1.24 (m, 6 H), 1.25−1.30 (m, 3H), 2.13 (s, 3H), 3.87 (m, 1H), 4.13−4.19 (m, 2H), 5.04 (s, 1 H), 11.10 (br, 1 H); ^{13}C NMR (90.5 MHz, $CDCl_3$) δ 13.9, 14.0, 21.0, 25.2, 29.0, 59.6, 92.4, 165.2, 168.0, 169.4; MS *m*/*z* 199, 184, 156, 111, 96, 70, 43; HRMS calcd for $C_{10}H_{18}NO_3$ 200.1287, found 200.1295.

(*E*)-Ethyl 4-Methyl-3-acetamido-2-pentenoate: ^{1}H NMR (200 MHz, acetone-d_6) δ 1.12 (d, *J* = 7.08 Hz, 6 H), 1.20 (t, *J* = 7.08 Hz, 3H), 2.08 (s, 3H), 4.05 (q, *J* = 7.09 Hz, 2H), 4.30 (m, 1H), 6.97 (s, 1 H), 8.14 (br, 1 H); ^{13}C NMR (50.3 MHz, acetone-d_6) δ 14.5, 19.6, 24.6, 27.7, 59.4, 100.8, 158.7, 168.3, 170.6; MS *m*/*z* 199, 184, 156, 113, 111, 96, 70, 43; HRMS calcd for $C_{10}H_{18}NO_3$ 200.1287, found 200.1286.

(*Z*)-Ethyl 3-Acetamido-2-hexenoate: ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.94 (t, *J* = 7.39 Hz, 3H), 1.27 (t, *J* = 7.11 Hz, 3H), 1.60 (m, 2H), 2.12 (s, 3H), 2.72 (t, 2H), 4.13 (t, *J* = 7.12 Hz, 2H), 4.92 (s, 1H), 11.10 (br, 1H); ^{13}C NMR (90.5 MHz, $CDCl_3$) δ 13.4, 14.0, 21.3, 25.1, 35.8, 59.6, 95.7, 158.7, 168.1, 169.1; MS *m*/*z* 199, 184, 170, 156, 129, 113, 96, 83, 43; HRMS calcd for $C_{10}H_{18}NO_3$ 200.1287, found 200.1290.

(*E*)-Ethyl 3-Acetamido-2-hexenoate: ^{1}H NMR (360 MHz, acetone-d_6) δ 1.15 (t, *J* = 7.39 Hz, 3H), 1.44 (t, *J* = 7.13 Hz, 3H), 1.53 (m, 2H), 2.28 (s, 3H), 2.95 (m, 2H), 4.30 (q, *J* = 7.14 Hz, 2H), 7.14 (s, 1H), 8.91 (br, 1H); ^{13}C NMR (90.6 MHz, acetone-d_6) δ 14.4, 15.1, 23.2, 25.1, 34.1, 59.9, 101.8, 155.4, 168.9, 170.8; MS *m*/*z* 199, 184, 170, 156, 156, 129, 112, 96, 83, 43; HRMS calcd for $C_{10}H_{18}NO_3$ 200.1287, found 200.1289.

(*Z*)-Isopropyl 3-Acetamido-2-butenoate: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.42−1.45 (m, 6H), 2.32 (s, 3H), 2.55 (m, 3H), 5.05 (s, 1H), 5.20 (m, 1H), 11.3 (br, 1H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 21.7, 21.8, 25.1, 67.0, 96.8, 154.5, 168.5, 168.7; MS *m*/*z* 185, 142, 126, 101, 83, 57, 43; HRMS calcd for $C_9H_{16}NO_3$ 186.1130, found 186.1130.

(*E*)-Isopropyl 3-Acetamido-2-butenoate: ^{1}H NMR (360 MHz, acetone-d_6) δ 1.10 (d, *J* = 6.33 Hz, 6H), 1.94 (s, 3H), 2.20 (s, 3H), 4.85 (m, 1H), 6.74 (s, 1H), 8.55 (br, 1H); ^{13}C NMR (90.6 MHz, acetone-d_6) δ 18.5, 22.6, 25.1, 66.9, 102.5, 151.1, 168.7, 170.5; MS *m*/*z* 185, 142, 126, 110, 83, 57, 43; HRMS calcd for $C_9H_{16}NO_3$ 186.1130, found 186.1130.

(*Z*)-Ethyl 3-Acetamido-2-butenoate: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.05−1.09 (m, 3H), 1.93 (s, 3H), 2.17 (s, 3H), 3.93−3.95 (m, 2H), 4.68 (s, 1H), 10.9 (br, 1H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 14.1, 21.7, 25.1, 59.7, 96.3, 154.9, 168.8, 169.0; MS *m*/*z* 171, 129, 98, 84, 69, 57, 43; HRMS calcd for $C_8H_{14}NO_3$ 172.0974, found 172.0976.

(*E*)-Ethyl 3-Acetamido-2-butenoate: ^{1}H NMR (360 MHz, acetone-d_6) δ 1.39 (t, *J* = 7.04 Hz, 3H), 2.23 (s, 3H), 2.49 (s, 3H), 4.25 (q, *J* = 7.27 Hz, 2H), 7.04 (s, 1H), 8.91 (br, 1H); ^{13}C NMR (90.6 MHz, acetone-d_6) δ 15.1, 18.5, 25.1, 59.9, 102.0, 151.4, 169.1, 170.6; MS *m*/*z* 171, 156, 129, 98, 84, 57, 43; HRMS calcd for $C_8H_{13}NO_3$ 171.0895, found 171.0900.

(*Z*)-Methyl 3-Acetamido-2-pentenoate: ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.03 (t, *J* = 7.35 Hz, 3H), 2.07 (s, 3H), 2.72 (m, 2H), 3.62 (s, 2H), 4.89 (s, 1H), 11.0 (br, 1H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 12.1, 24.8, 26.9, 50.5, 93.9, 160.3, 167.9, 169.4; MS *m*/*z* 171, 140, 129, 98, 84, 69, 43; HRMS calcd for $C_8H_{13}NO_3$ 171.0895, found 171.0898.

(*E*)-Methyl 3-Acetamido-2-pentenoate: ^{1}H NMR (360 MHz, acetone-d_6) δ 1.21 (t, *J* = 7.52 Hz, 3H), 2.15 (s, 3H), 2.84 (q, *J* = 7.47 Hz, 2H), 3.69 (s, 2H), 6.96 (s, 1H), 8.80 (br, 1H); ^{13}C NMR (90.6 MHz, acetone-d_6) δ 13.2, 24.4, 25.0, 50.4, 99.9, 156.6, 168.5, 170.3; MS *m*/*z* 171, 140, 129, 112, 98, 84, 69, 43; HRMS calcd for $C_8H_{13}NO_3$ 171.0895, found 171.0890.

(*E*)-Methyl 5-Methyl-3-acetamido-2-hexenoate:[4a] ^{1}H NMR (360 MHz, acetone-d_6) δ 1.01 (d, *J* = 6.72 Hz, 6H), 2.13−2.15 (m, 3H), 2.79 (d, *J* = 7.44 Hz, 2H), 3.68 (s, 3H), 7.07 (s, 1H), 8.75 (br, 1H).

Methyl 3-Acetamido-3-phenyl-2-propenoate:[4a] ^{1}H NMR (200 MHz, $CDCl_3$) δ (*Z* isomer) 2.17 (s, 3H), 3.77 (s, 3H), 5.29 (s, 1H), 7.37−7.45 (m, 5H); (*E* isomer) 2.38 (s, 3H), 3.77 (s, 3H), 6.65 (s, 1H), 7.37−7.45 (m, 5H).

General Procedure for Asymmetric Hydrogenation. To a solution of $[Rh(COD)_2]OTf$ (2.0 mg, 4.27×10^{-3} mmol) in toluene (3.4 mL) in a glovebox was added the chiral ligand (0.047 mL of a 0.1 M solution in toluene, 4.7×10^{-3} mmol). After the mixture was stirred for 30 min, substrate **1** (0.427 mmol) was added. The hydrogenation was performed at rt under 10 atm of hydrogen for 24 h. The hydrogen pressure was released carefully in a hood, and the reaction mixture was passed through a short silica gel column to remove the catalyst. The enantiomeric excesses were measured by GC without further purification.

(*R*)-Methyl 3-Acetamidobutanoate:[4a,b] $[\alpha]^{25}_D = +21.4$ (*c* 1.4, MeOH); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.16 (d, *J* = 6.81 Hz, 3 H), 1.90 (s, 3H), 2.47 (m, 3H), 3.63 (s, 3H), 4.28 (m, 1H), 6.14 (br, 1H).

(*S*)-Ethyl 4-Methyl-3-acetamidopentanoate: $[\alpha]^{25}_D = +52.8$ (*c* 1.2, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.83−0.86 (m, 6 H), 1.15−1.20 (m, 3H), 1.75 (m, 1H), 1.90 (s, 3H), 2.40−2.43 (m,

2H), 4.00−4.08 (m, 3H), 639 (br, 1 H); ^{13}C NMR (90.5 MHz, $CDCl_3$) δ 13.9, 18.5, 19.0, 23.0, 31.3, 36.5, 51.3, 60.3, 169.4, 171.8; MS *m*/*z* 202, 186, 158, 142, 116, 97, 70, 43; HRMS calcd for $C_{10}H_{20}NO_3$ 202.1443, found 202.1452.

(*R*)-Ethyl 3-Acetamidohexanoate: $[\alpha]^{25}_D = +42.8$ (*c* 1.86, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85 (t, $J = 6.92$ Hz, 3H), 1.16−1.45 (m, 7H), 1.91 (s, 3H), 2.43−2.46 (m, 2H), 4.06 (q, $J = 7.14$ Hz, 2H), 4.14−4.28 (m, 1H), 6.25 (br, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 13.7, 14.0, 19.3, 23.2, 36.1, 38.5, 45.7, 60.4, 169.5, 171.8; MS *m*/*z* 201, 186, 172, 158, 142, 116, 97, 72, 43; HRMS calcd for $C_{10}H_{20}NO_3$ 202.1443, found 202.1450.

(*R*)-Isopropyl 3-Acetamidobutanoate: $[\alpha]^{25}_D = +35.5$ (*c* 1.91, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.13−1.18 (m, 6H), 1.88 (s, 3H), 2.37−2.47 (m, 2H), 4.24−4.28 (m, 1H), 4.92−4.96 (m, 1H), 6.59 (br, 1H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 19.8, 21.47, 21.53, 23.0, 40.4, 42.0, 67.7, 169.2, 170.9; MS *m*/*z* 187, 144, 128, 102, 86, 69, 43; HRMS calcd for $C_9H_{18}NO_3$ 188.1288, found 188.1287.

(*R*)-Ethyl 3-Acetamidobutanoate: $[\alpha]^{25}_D = +41.9$ (*c* 1.69, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.15 (t, $J = 6.78$ Hz, 3H), 1.18 (t, $J = 7.08$ Hz, 3H), 1.88 (s, 3H), 2.41−2.44 (m, 2H), 4.06 (q, $J = 7.15$ Hz, 2H), 4.22−4.30 (m, 1H), 6.42 (br, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.0, 19.8, 23.2, 40.0, 41.9, 60.4, 169.3, 171.5; MS *m*/*z* 173, 158, 130, 116, 86, 70, 43; HRMS calcd for $C_8H_{15}NO_3$ 174.1130, found 174.1136.

(*R*)-Methyl 3-Acetamidopentanoate: $[\alpha]^{25}_D = +52.0$ (*c* 1.26, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.85 (t, $J = 7.49$ Hz, 3H), 1.45−1.54 (m, 2H), 1.91 (s, 3H), 2.46−2.50 (m, 2H), 3.61 (s, 3H), 4.06−4.12 (m, 1H), 6.20 (br, 1H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 10.5, 23.2, 27.0, 37.9, 47.4, 51.5, 169.6, 172.1; FAB-MS 174 ($M^+ + 1$); HRMS calcd for $C_8H_{15}NO_3$ 174.1130, found 174.1133.

(*R*)-Methyl 5-Methyl-3-acetamidohexanoate:[4a] $[\alpha]^{25}_D = +44.6$ (*c* 1.56, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.89−0.91 (m, 6H), 1.20−1.35 (m, 1H), 1.45−1.70 (m, 2H), 1.96 (s, 3H), 2.44−2.60 (m, 2H), 3.68 (s, 3H), 4.28−4.35 (m, 1H), 5.98 (br, 1H).

(*S*)-Methyl 3-Acetamido-3-phenylpropanoate:[4a] $[\alpha]^{25}_D = -40.5$ (*c* 2.15, MeOH); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.92 (s, 3H), 2.76−2.83 (m, 2H), 3.53 (s, 3H), 5.34 (m, 1H), 6.65 (br, 1H), 7.18−7.27 (m, 5H).

Determination of Enantiomeric Excesses: Chiral Capillary GC Column. Chiral Select-1000 column (dimensions 15 m × 0.25 mm (i.d.)) or γ-DEX 225 column (dimensions 30 m × 0.25 mm (i.d.)). Carrier gas: He (1 mL/min). The racemic products were obtained by hydrogenation of substrates with an achiral catalyst. The following are the retention times for the racemic products.

Methyl 3-Acetamidobutanoate: (capillary GC, Chiral Select-1000 column, 130 °C, isothermal) (*S*) $t_1 = 6.94$ min, (*R*) $t_2 = 8.29$ min.

Ethyl 4-Methyl-3-acetamidopentanoate: (capillary GC, γ-DEX 225 column, 145 °C, isothermal) (*S*) $t_1 = 18.81$ min, (*R*) $t_2 = 19.38$ min.

Methyl 4, 4-Dimethyl-3-acetamidopentanoate: (capillary GC, γ -DEX 225 column, 150 °C, isothermal) (*S*) $t_1 = 14.13$ min, (*R*) $t_2 = 14.78$ min.

Ethyl 3-Acetamidohexanoate: (capillary GC, γ-DEX 225 column, 140 °C, isothermal) (*S*) $t_1 = 25.72$ min, (*R*) $t_2 = 26.24$ min.

Isopropyl 3-Acetamidobutanoate: (capillary GC, Chiral Select-1000 column, 140 °C, isothermal) (*S*) $t_1 = 6.63$ min, (*R*) $t_2 = 7.33$ min.

Ethyl 3-Acetamidobutanoate: (capillary GC, Chiral Select-1000 column, 140 °C, isothermal) (*S*) $t_1 = 6.05$ min, (*R*) $t_2 = 6.67$ min.

Methyl 3-Acetamidopentanoate: (capillary GC, γ-DEX 225 column, 145 °C, isothermal) (*R*) $t_1 = 12.28$ min, (*S*) $t_2 = 12.63$ min.

Methyl 5-Methyl-3-acetamidohexanoate: (capillary GC, γ-DEX 225 column, 145 °C, isothermal) (*S*) $t_1 = 17.20$ min, (*R*) $t_2 = 17.70$ min.

Methyl 3-Acetamido-3-phenylpropanoate: (capillary GC, Chiral Select-1000 column, 180 °C, isothermal) (*S*) $t_1 = 8.88$ min, (*R*) $t_2 = 9.32$ min.

Acknowledgment. This work was supported by a Camille and Henry Dreyfus New Faculty Award and Teaching-Scholar Award, an ONR Young Investigator Award, a DuPont Young Faculty Award, Catalytica Pharmaceuticals, and DuPont Agricultural Products. We acknowledge a generous loan of precious metals from Johnson Matthey, Inc. and a gift of chiral GC columns from Supelco. We thank Dr. Mark A. Scialdone of DuPont Central Research & Development for valuable discussions and encouragement.

Supporting Information Available: NMR spectra for the compounds used in this study. This material is available free of charge via the Internet at http://pubs.acs.org.

JO990565H