Highly Enantioselective Rhodium-Catalyzed Hydrogenation of Dehydroamino Acids with New Chiral Bisphosphinites

Guoxin Zhu and Xumu Zhang*

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

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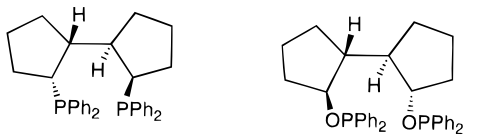
Asymmetric synthesis based on transition metal catalyzed processes has attracted a great deal of interest because of its high efficiency for the preparation of enantiomerically pure compounds. The development of efficient chiral transition metal complexes has focused mainly on the design and synthesis of new chiral ligands. Many chiral bisphosphines[1] have been invented to facilitate enantioselective catalytic reactions, and unique properties of chiral ligands are strongly associated with their ligand frameworks such as biaryl chirality with BINAP and chiral phosphalane with DuPhos. Recently, we have reported a new chiral 1,4-bisphosphine, (2*R*,2′*R*)-bis(diphenylphosphino)-(1*R*,1′*R*)-dicyclopentane (**1**) [(1*R*,1′*R*,2*R*,2′*R*)-BICP] (Figure 1) for the effective rhodium-catalyzed asymmetric hydrogenation of α-(acylamino)-acrylic acids.[2] This new chiral phosphine has four stereogenic centers, and contains two cyclopentane rings in its backbone which greatly restrict its conformational flexibility. A recent work by Chan et al.[3m] also concurs with our observation that increasing ligand rigidity is the key for the development of highly enantioselective reactions.

In contrast to many chiral phosphines reported in the literature, phosphinites used in metal complexes for asymmetric reactions are generally rather poor ligands with few exceptions.[3] While phosphinites are less electron donating than phosphines, they can be excellent ligands for asymmetric hydroformylation[4] and hydrocyanation reactions.[5] *Clearly, it is worthwhile to search for new chiral phosphinites with new chiral scaffolds.* Taking advantage of the relatively rigid biscyclopentane backbone of BICP, we made the corresponding chiral bisphosphinite, (2*S*,2′*S*)-bis(diphenylphosphinoxy)-(1*R*,1′*R*)-dicyclopentane (abbreviated (1*R*,1*R*′,2*S*,2′*S*)-BICPO) (Figure 1), from (1*R*,1′*R*)-bicyclopentyl-(2*S*,2′*S*)-diol. Highly enantioselective hydrogenation of dehydroamino acids catalyzed by rhodium complexes with this ligand is reported herein. Our goal is not simply to create another asymmetric catalytic system for hydrogenation of dehydroamino acids—a well-studied reaction—the impact of this study is to enhance fundamental understanding of those factors in chiral ligand design by exploring a variety of chiral ligand motifs.



(1R, 1'R, 2R, 2'R)-BICP **1** (1R, 1'R, 2S, 2'S)-BICPO **2**

Figure 1.

The bisphosphinite ligand (**2**, (1*R*,1′*R*,2*S*,2′*S*)-BICPO) is easily made from chiral (1*R*,1′*R*)-bicyclopentyl-(2*S*,2′*S*)-diol **3** in high yield as illustrated in Scheme 1.

The cationic Rh(I) complex [Rh(COD)(BICPO)]BF_4, prepared in situ by mixing [$Rh(COD)_2$]BF_4 with 1.1 molar equiv of (1*R*,1′*R*,2*S*,2′*S*)-BICPO under an inert atmosphere, is a highly effective catalyst for the hydrogenation of α-acetoamidocinnamic acid at ambient temperature under 1 atm of H_2. Table 1 summarizes the results of hydrogenation of α-acetoamidocinnamic acid under a variety of experimental conditions. The reaction medium significantly affects the catalytic activity and enantioselectivity of the product. Unlike our early observation on the additive effect of triethylamine with the BICP system,[2] the enantioselectivity and reactivity of the hydrogenation decreased drastically in the presence of a catalytic amount of triethylamine (Rh:**2**:Et_3N = 1:1.1:50).[6] For example, α-acetoamidocinnamic acid was completely reduced with 89.1% ee in THF in the absence of Et_3N, while only 30% was reduced with 30.9% ee with a catalytic amount of Et_3N under 1 atm of H_2 (entry 3 vs 2, entry 5 vs 4). Asymmetric hydrogenation in alcoholic solvents (entries 4, 6, and 8−9), except with CF_3CH_2OH (entry 7), gave better selectivities than in THF (entry 2) and $ClCH_2CH_2Cl$ (entry 1). Among several common alcohol solvents, the highest enantioselectivity (94.7% ee, *S*) for the hydrogenation of α-acetoamidocinnamic acid was achieved in ^{i}PrOH under 1 atm of H_2 at ambient temperature (entry 9). The best result (96.1% ee, 100% conversion) for the hydrogenation of α-acetoamidocinnamic acid was obtained when (1*R*,1′*R*,2S,2′S)-BICPO

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Scheme 1

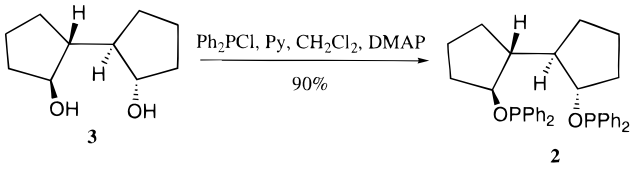
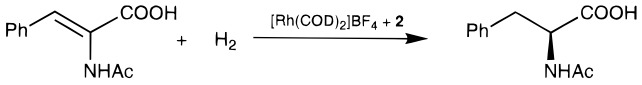


Table 1. Rh-Catalyzed Asymmetric Hydrogenation of α-Acetamidocinnamic Acid[a]



entry	solvent	Et_3N (%)	Con. (%)[b]	ee (%)[b]
1	$ClCH_2CH_2Cl$		100	88.2
2	THF		100	89.1
3	THF	50	30	30.9
4	MeOH		100	92.4
5	MeOH	50	100	67.9
6	EtOH		100	92.0
7	CF_3CH_2OH		100	80.3
8	^{t}BuOH		100	91.1
9	^{i}PrOH		100	94.7
10[c]	^{i}PrOH		100	96.1
11[d]	^{i}PrOH		86.6	63.9

[a] The reaction was carried out at rt under 1 atm of H_2 for 24 h [substrate (0.5 mmol, 0.125 M):$[Rh(COD)_2]BF_4$:ligand(**2**) = 1:0.01:0.011]. [b] Determined by GC using a Chirasil-VAL III FSOT column on the corresponding methyl ester. The *S* absolute configuration was determined by comparing the optical rotation with the reported value.[10j] [c] Reaction was carried out at 0 °C. [d] $[Rh(COD)Cl]_2$ (0.5 mol %) was used as the catalyst precursor.

was used in ^{i}PrOH under 1 atm of H_2 at 0 °C (entry 10). A neutral rhodium catalyst formed in situ from **2** and $[Rh(COD)Cl]_2$ is less effective than the cationic one described above (entry 11).

Four stereogenic carbon centers are contained within our ligand system, which is fundamentally distinct from either axially dissymmetric BINAP, planar chiral phosphines, or other diphosphines with two stereogenic carbon centers in their backbone. The absolute configurations at the 2,2′-positions are opposite in BICP (**1**) and BICPO (**2**), but in the asymmetric hydrogenation of α-acetoamidocinnamic acid, both gave the same amino acid: (*S*)-*N*-acetylphenylalanine. These results suggest that these reactions, promoted by a seven-membered (1*R*,1′*R*,2*R*,2′*R*)-BICP−Rh complex and a nine-membered (1*R*,1′*R*,2*S*,2′*S*)-BICPO−Rh complex, may proceed via different pathways. It is apparent that there must be careful matching of the catalyst chiral environment to the substrate in order to obtain high selectivity. To further understand the relationship between the absolute configuration of BICPO (**2**) and the product stereochemistry, the absolute configurations of the 2,2′-positions of diol (1*R*,1′*R*,2*S*,2′*S*)-**3** was converted into (1*R*,1′*R*,2*R*,2′*R*)-**4** via a Mitsunobu reaction.[7] A new bisphosphinite, (1*R*,1′*R*,2*R*,2′*R*)-**5,** having the same configuration as the original (1*R*,1′*R*,2*R*,2′*R*)-BICP was made (Scheme 2). Using (1*R*,1′*R*,2*R*,2′*R*)-**5** as the ligand under the best conditions for hydrogenation with (1*R*,1′*R*,2S,2′S)-**2**, α-acetoamidocinnamic acid was reduced completely with slightly lower enantioslectivity (83.5% ee) to give (*R*)-*N*-acetylphenylalanine as the product.

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Scheme 2

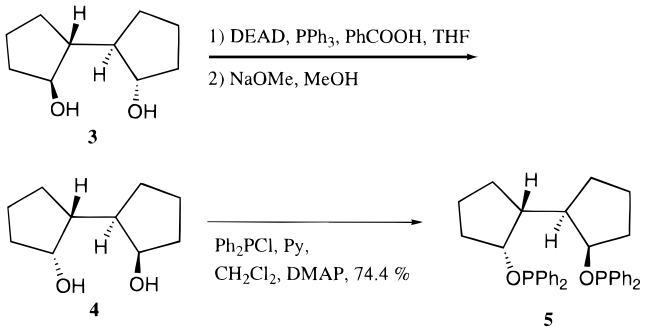
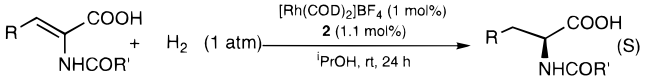


Table 2. Asymmetric Hydrogenations of Dehydroamino Acid Derivatives



entry	substrate	% ee[a]
1	R = H, R′ = CH_3	94.8
2	R = Ph, R′ = CH_3	94.7
3	R = Ph, R′ = Ph	89.2
4	R = *m*-Br-C_6H_4, R′ = CH_3	93.5
5	R = *o*-Cl-C_6H_4, R′ = CH_3	92.9
6	R = *p*-F-C_6H_4, R′ = CH_3	91.1
7	R = *p*-MeO-Ph, R′ = CH_3	93.2[b]
8	R = *p*-OAc-*m*-OMePh, R′ = CH_3	95.0[b]
9	R = 2-naphthyl, R′ = CH_3	91.4
10	R = 2-thienyl, R′ = CH_3	90.1
11	R = *i*-Pr, R′ = CH_3	45.7

[a] The *S* absolute configurations were determined by comparing optical rotations with reported values. The % ee was determined by GC using a Chirasil-VAL III FSOT column on the corresponding methyl ester. The reaction went in quantitative yield. [b] The % ee was determined by HPLC using a Chiralcel OJ column on the corresponding methyl esters.

Several dehydroamino acids were hydrogenated with the Rh−(1*R*,1′*R*,2*S*,2′*S*)-BICPO catalyst (Table 2). High selectivity was achieved for the hydrogenation of α-(acetoamido)acrylic acid (94.8% ee, entry 1 in Table 2). Over 90% ee's have been obtained for many substituted α-acetoamidocinnamic acids. The enantioselectivity for the hydrogenation of dehydro-*N*-acetylleucine was lower than for other substrates (entry 11 in Table 2). Compared with Rh−BICP **1** catalyst, the enantioselectivity with Rh−BICPO **2** is slightly inferior, i.e., about 2−10% reduction in ee for substrates listed in entries 1−4, 7, and 8 in Table 2. A striking difference was found for the hydrogenation of dehydro-*N*-acetylleucine (entry 11, 47% ee decrease with Rh−BICPO **2**). The overall enantioselectivities are comparable with enantioselectivities attained previously with the best chiral bisphosphines or bisphosphinites,[3j,m,8] which form five- to seven-membered ring complexes with

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transition metals. However, compared with the potential nine-membered chelated bidentate ligands reported by Grubbs,[3b] Miyano,[9] and Kumada,[10] our new bisphosphinites **2** and **3** display the highest reactivities and enantioselectivities in the rhodium-catalyzed asymmetric hydrogenation of α-(acylamino)acrylic acids.

Conclusions

The mechanism of asymmetric hydrogenation of dehydroamino acids has been examined intensively.[11] It is generally accepted that a chiral ligand which can form a rigid ligand−metal complex is essential for effective chiral recognition. The most difficult part of research in asymmetric catalysis is to find effective new ligand scaffolds. Our study shows that the new class of phosphinites **2** and **3,** which could potentially form nine-membered chelated complexes with rhodium, gave remarkably high selectivities for the hydrogenation of dehydroamino acids. The key element of this system is that the two cyclopentane rings in the backbone restrict the conformational flexibility of the nine-membered ring, and the four stereogenic carbon centers in the backbone dictate the orientation of four *P*-phenyl groups. Other chiral ligands based on this framework are under study and will be reported in due course.

Experimental Section

General. All reactions and manipulations were performed in a nitrogen-filled glovebox or using standard Schlenk techniques. Toluene, benzene, and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl under nitrogen. Methylene chloride and 1,2-dichloroethane were distilled from CaH_2. Methanol, ethnaol, and 2-propanol were distilled from Mg under nitrogen. Column chromatography was performed using EM Silica gel 60 (230−400 mesh).

α-Acetamidoacrylic acid and its methyl ester were purchased from Aldrich and used as received. All other substrates, *β*-isopropyl-α-acetoamidoacrylic acid,[12] α-benzoamidocinnamic acid,[13] methyl α-benzoamidocinnamate,[14] *β*-aryl-α-acetoamidoacrylic acid,[15] and their methyl esters,[14] were prepared by standard Erlenmeyer procedures. (1*R*,1′*R*)-Bicyclopentyl-(2*S*,2′*S*)-diol **(3)** was made according to the previous reported procedure.[2]

(2*S*,2′*S*)-Bis(diphenylphosphinoxy)-(1*R*,1′*R*)-dicyclopentane (2). To a solution of (1*R*,1′*R*)-bicyclopentyl-(2*S*,2′*S*)-diol (**3**) (0.51 g, 3.0 mmol) and DMAP (36 mg, 0.3 mmol) in CH_2Cl_2 (5 mL) was added pyridine (4.86 mL, 60 mmol) under stirring. Then the mixture was cooled to 0 °C, and a solution of $ClPPh_2$ (1.24 mL, 6.9 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The mixture was stirred at 0 °C for 5 h, followed by 48 h at room temperature. Then the reaction mixture was concentrated under vacuum and excess chlorodiphenylphosphine, pyridine HCl salt, and phosphorus impurities were removed by filtration through basic alumina (1 × 5 cm), eluted with ether (3 × 20 mL). The solvents were removed from the filtrate under reduced pressure to afford desired phosphinite **2** (1.45 g, 90.0% yield): ^{1}H NMR ($CDCl_3$) *δ* 7.50−7.43 (m, 8 H), 7.36−7.26 (m, 12 H), 4.22−4.20 (m, 2 H), 2.15 (m, 2 H), 1.82−1.66 (m, 8 H), 1.59−1.53 (m, 2 H), 1.28−1.21 (m, 2H); ^{31}P NMR ($CDCl_3$) *δ* P = 106.7; ^{13}C NMR ($CDCl_3$) *δ* 143.18−142.70 (m), 130.38−130.07 (m), 128.90 (s, 128.18−128.08 (m), 85.56 (d, *J* = 17.9 Hz), 49.29 (d, *J* = 6.52 Hz), 33.78 (d, *J* = 5.61 Hz), 27.06 (s), 22.59 (s). MS *m/z*: 538, 461, 383, 353, 337, 201, 185, 151, 135, 77; HRMS calcd for $C_{34}H_{36}O_2P_2$ (M^+) 538.2190, found 538.2156.

(1*R*,1′*R*)-Bicyclopentyl-(2*R*,2′*R*)-diol (4). Under nitrogen, to a solution of diol **2** (2.5 g, 14.7 mmol), benzioc acid (7.26 g, 59.4 mmol), and triphenylphosphine (15.6 g, 59.5 mmol) in THF (50 mL) was added diethyl azodicarboxylate (9.4 mL, 59.7 mmol) dropwise at 0 °C. After stirring overnight at room temperature, the solution was concentrated and the residue was chromatographed on silica gel to afford the benzoate ester. The benzoate ester was directly used for hydrolysis. A mixture of NaOMe, which was made from sodium (3.35 g, 0.15 mol) and MeOH (560 mL), and benzoate ester in MeOH was stirred overnight at room temperature. After evaporation of MeOH, the residue was diluted with ether and water and acidified with 10% aqueous hydrochloric acid. The mixture was extracted with methylene chloride, and the combined organic layer was dried over sodium sulfate. After evaporation of solution, the residue was purified by chromatography on silica gel. Diol **4** was obtained as a solid (1.0 g, 40% total yield): $[\alpha]^{25}_D = -54.0$ (*c*, 1.07, $CHCl_3$); ^{1}H NMR ($CDCl_3$) *δ* 4.30−4.28 (m, 2H), 1.87−1.49 (m, 14 H); ^{13}C NMR ($CDCl_3$) *δ* 74.21, 45.59, 35.23, 28.27, 21.62. MS *m/z* 152, 134, 121, 108, 67, 41, 37; HRMS calcd for $C_{10}H_{17}O$ (M^+ − OH) 153.1279, found 153.1238.

(2*R*,2′*R*)-Bis(diphenylphosphinoxy)-(1*R*,1′*R*)-dicyclopentane (5). This compound was made in a similar fashion as phosphinite **2** (1.20 g, 74.4% yield): ^{1}H NMR ($CDCl_3$) *δ* 7.48−7.40 (m, 8 H), 7.35−7.27 (m, 12 H), 4.11−4.09 (m, 2 H), 1.86−1.70 (m, 8 H), 1.58−1.50 (m, 4 H), 1.50−1.30 (m, 2H); ^{31}P NMR ($CDCl_3$) *δ* 106.1; ^{13}C NMR ($CDCl_3$) *δ* 143.79−142.70 (m), 131.19−127.99 (m), 83.44 (dd, J_1 = 2.01 Hz, J_2 = 19.4 Hz), 46.03 (d, *J* = 6.44 Hz), 33.42 (d, *J* = 4.98 Hz), 28.30 (s), 21.58 (s). MS *m/z* 538, 461, 383, 353, 337, 269, 201, 185, 151, 135, 77; HRMS calcd for $C_{34}H_{36}O_2P_2$ (M^+) 538.2190, found 538.2159.

General Procedure for Asymmetric Hydrogenation. In a glovebox, to a solution of $[Rh(COD)_2]BF_4$ (5.0 mg, 0.012 mmol) in MeOH (10 mL) was added chiral ligand **2** (0.15 mL of 0.1 M solution in toluene, 0.015 mmol). After stirring the mixture for 30 min, the dehydroamino acid (1.2 mmol) was added. The hydrogenation was performed at room temperature under 1 atm of hydrogen for 24 h. The reaction mixture was treated with CH_2N_2 and then concentrated in vacuo. The residue was passed through a short silica gel column to remove the catalyst. The enantiomeric excesses were measured by capillary GC or HPLC. The absolute configuration of products was determined by comparing the observed rotation with the reported value.[8d,j]

Determination of Enantiomeric Excess. Chiral capillary GC used the following: column, Chirasil-VAL III FSOT; dimensions, 25 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 is the retention time for the racemic products.

***N*-Acetylphenylalanine methyl ester:**[8j] (capillary GC, 150 °C, isothermal) (*R*) t_1 = 14.66 min, (*S*) t_2 = 16.23 min; ^{1}H NMR ($CDCl_3$) *δ* 7.34−7.06 (m, 5H), 5.93 (br, 1H), 4.93−4.83 (m, 1H), 3.72 (m, 3H), 3.14−3.06 (m, 2H), 1.98 (s, 3H).

***N*-Acetylalanine methyl ester:**[8j] (capillary GC, 100 °C, isothermal) (*R*) t_1 = 5.56 min, (*S*) t_2 = 6.73 min; ^{1}H NMR ($CDCl_3$) *δ* 6.07 (br, 1H), 4.60 (q, *J* = 7.21 Hz, 1H), 3.75 (s, 3H), 2.01 (s, 3H), 1.40 (d, *J* = 7.10 Hz, 3H).

***N*-Acetyl-*m*-bromophenylalanine methyl ester:**[8j] (capillary GC, 180 °C, isothermal) (*R*) t_1 = 14.14 min, (*S*) t_2 = 15.09 min; ^{1}H NMR ($CDCl_3$) *δ* 7.50−7.00 (m, 4 H), 6.03−5.98 (br, 1H), 4.89−4.79 (m, 1H), 3.80 (s, 3H), 3.08 (m, 2H), 1.85 (s, 3H).

***N*-Benzoylphenylalanine methyl ester:**[8j] (capillary GC, 180 °C, isothermal) (*R*) t_1 = 35.65 min, (*S*) t_2 = 37.13 min; ^{1}H NMR ($CDCl_3$) *δ* 7.80−7.10 (m, 10 H), 6.65−6.55 (br, 1H), 5.14−5.05 (m, 1 H), 3.76 (s, 3H), 3.36−3.17 (m, 2H).

***N*-Acetylleucine methyl ester:**[8j] (capillary GC, 110 °C, isothermal) (*R*) t_1 = 16.1 min, (*S*) t_2 = 19.4min; ^{1}H NMR ($CDCl_3$)

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δ 5.93 (br, 1H), 4.62 (m, 1H), 3.72 (s, 3H), 1.98 (s, 3H), 1.70−1.50 (m, 3H), 1.04 (d, J = 6.63 Hz, 3 H), 0.90 (d, J = 7.0 Hz, 3H).

***N*-Acetyl-*p*-fluorophenylalanine methyl ester:**[8j] (capillary GC, 180 °C, isothermal) (*R*) t_1 = 5.02 min, (*S*) t_2 = 5.28 min; ^{1}H NMR ($CDCl_3$) δ 7.07−6.95 (m, 4 H), 5.92 (br, 1H), 4.88−4.83 (m, 1H), 3.72 (s, 3H), 3.16−3.03 (m, 2H), 1.95 (s, 3H).

***N*-Acetyl-*o*-chlorophenylalanine methyl ester:**[8j] (capillary GC, 180 °C, isothermal) (*R*) t_1 = 9.32 min, (*S*) t_2 = 9.78 min.

***N*-Acetyl-3-(2-naphthyl)alanine methyl ester:** (capillary GC, 190 °C, isothermal) (*R*) t_1 = 27.88 min, (*S*) t_2 = 29.30 min; ^{1}H NMR ($CDCl_3$) δ 7.32−7.30 (m, 1 H), 7.17−7.12 (m, 3H), 6.33−6.30 (br, 1H), 4.90−4.84 (m, 1H), 3.67 (s, 3H), 3.30−3.24 (m, 1H), 3.15−3.09 (m, 1H), 1.92 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.05, 169.71, 134.33, 134.08, 131.16, 129.51, 128.42, 126.78, 52.29, 35.32, 22.84, 0.89; MS *m*/*z* 258 (M^+ + ^{37}Cl), 256 (M^+ + ^{35}Cl), 226, 224, 216, 214, 198, 196, 161, 156, 154 125, 118, 102, 91, 88; HRMS calcd for $C_{12}H_{14}ClNO_3$ 255.0662 (M^+), found 255.0655.

***N*-Acetyl-3-(2-thienyl)alanine methyl ester:**[8j] (capillary GC, 170 °C, isothermal) (*R*) t_1 = 7.21 min, (*S*) t_2 = 7.54 min; ^{1}H NMR ($CDCl_3$) δ 7.20−7.00 (m, 3H), 6.10 (br, 1H), 4.90−4.87 (m, 1H), 3.76 (s, 3H), 3.40−3.38 (m, 2H), 2.00 (s, 3H).

Chiral HPLC used the following: column, Daicel Chiralcel OJ (*p*-toloyl cellulose ester coated on silica gel); particle size, 5.0 μm; dimensions, 25 cm (length) × 0.46 cm (i.d.); column temperature, 25 °C.

***N*-Acetyl-*p*-methoxyphenylalanine methyl ester:**[8j] (HPLC, 1.0 mL/min, 10% 2-PrOH/hexane) (*S*) t_1 = 62.52 min, (*R*) t_2 = 72.45 min; ^{1}H NMR ($CDCl_3$) δ 7.01−6.95 (m, 2H), 6.85−6.77 (m, 2H), 5.90 (br, 1H), 4.86−4.77 (m, 1H), 3.69 (s, 3H), 3.75 (s, 3H), 3.02 (dd, J_1 = 2.23 Hz, J_2 = 5.73 Hz, 2H), 1.94 (s, 3H).

***N*-Acetyl-*p*-acetoxy-*m*-methoxyphenylalanine methyl ester:**[8d] (HPLC, 1.0 mL/min, 10% 2-PrOH/hexane) (*R*) t_2 = 70.75 min, (*S*) t_1 = 73.70 min; ^{1}H NMR ($CDCl_3$) δ 6.94 (d, J = 8.0 Hz, 1H), 6.92−6.63 (m, 2H), 6.00−5.97 (br, 1H), 4.90−4.84 (m, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.11 (m, 2H), 2.29 (s, 3H), 1.99 (s, 3H).

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Supporting Information Available: Spectroscopic data for compounds **2**−**4** and details for the determination of enantiomeric excess (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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