Highly Enantioselective Synthesis of α,*β*-Diaminopropanoic Acid Derivatives Using a Catalytic Asymmetric Hydrogenation Approach

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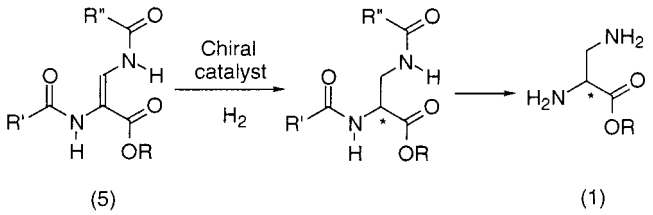
Rh-DuPhos-catalyzed asymmetric hydrogenation of α,*β*-diamidoacrylates provides a highly efficient and enantioselective route to chiral α,*β*-diaminopropanoic acid derivatives. The mechanistic course of the hydrogenation was studied using isotopically enriched enamide complexes and phosphorus and carbon NMR. Addition of methyl α-*N*-benzoyl-*β*-*N*-acetyl-diaminopropenoate to the solvated catalyst gave a single 1:1 enamide complex and demonstrated the binding of the olefin and α-amide carbonyl group; the carboxylate and *β*-*N*-acyl groups did not bind to the metal. Changes to the electronic and steric properties of the *β*-*N*-acyl group were well tolerated; however, small changes to the binding α-*N*-acyl group were found to significantly affect hydrogenation yields.

Introduction

The recent development of several Rh-bisphosphine catalysts has significantly expanded the synthetic utility of asymmetric hydrogenation.[1] For example, highly efficient and selective routes to chiral alcohols,[2] amines,[3] and α-amino acids[4] have been accomplished through hydrogenation of enol acetates, *N*-acylhydrazones, and *N*-acylamino acrylates. We were interested in applying this methodology to the synthesis of α,*β*-diaminopropanoates (1) (DAP). This diamine is a structural component of several natural products, such as bleomycin,[5] sulfazecin,[6] and capreomycin[7] and can be used in the construction of azetidinones,[8] protease inhibitors,[9] and peptides.[10] Existing routes to this molecule utilize α-amino acid starting materials. For example, Mitsunobu reactions on serine,[11] Hofmann and Curtius rearrangements of asparagine derivatives,[12] and Schmidt reactions of aspartic acid[13] have all been used to access chiral α,*β*-diaminopropanoic acid. Many of these routes, however, are marred by poor yields and/or protecting group sensitivity. We believed that a catalytic asymmetric hydrogenation approach to DAP would provide an efficient route to α,*β*-diaminopropanoates and also allow equal access to the orthogonally *N*-protected (*S*)- and (*R*)-isomers (Scheme 1).

Scheme 1



Results and Discussion

Synthesis of the Hydrogenation Substrates. The required α,*β*-diamidopropenoate substrates were readily synthesized in three steps from *N*-acyl-protected glycine (**2**) (Scheme 2). Hence, condensation of hippuric acid (**2**, R′ = Ph) with dimethylformamide dimethylacetal first gave *β*-*N*,*N*-(dimethylamino)-α,*β*-dehydroamino acid methyl ester (**3**) in 75% yield.[14] *N*-Benzoylglycine methyl ester was an isolated byproduct of this reaction and was easily separated from the required enamine (**3**) via trituration. The use of diethylformamide diethylacetal similarly afforded the ethyl ester derivative in 68% yield. Under mild amination conditions, the primary enamines (**4**) were prepared in excellent yield by treatment of the

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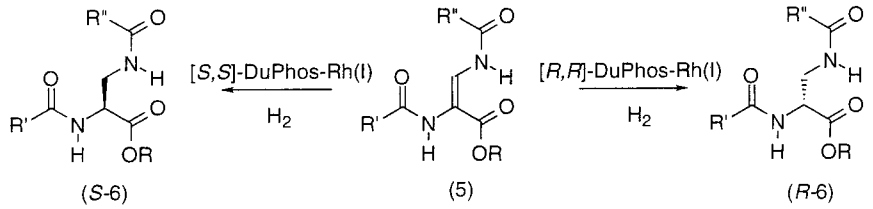
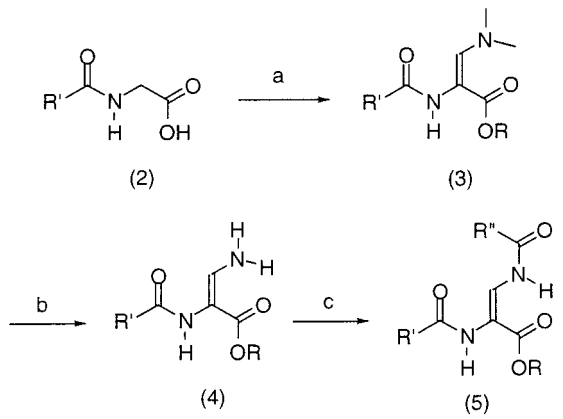
Table 1. Rh-Catalyzed Asymmetric Hydrogenation of α,β-Diamidopropenoates



entry	substrate[a]	R′	R″	catalyst	solvent	% yield[b] (**6**)	% ee	absolute configuration
1	**3**	Ph	-	*R*,*R*-Et-DuPhos	MeOH	0	-	-
2	**4**	Ph	-	*R*,*R*-Et-DuPhos	MeOH	0	-	-
3	**4**·HCl	Ph	-	*R*,*R*-Et-DuPhos	MeOH	0[c]	-	-
4	**5a**	Ph	Me	*R*-(+)-BiNAP	MeOH	5	-	-
5	**5a**	Ph	Me	(+)-DIOP	MeOH	5	-	-
6	**5a**	Ph	Me	*R*,*R*-Et-DuPhos	MeOH	100	99	*R*
7	**5a**	Ph	Me	*S*,*S*-Et-DuPhos	MeOH	100	99	*S*
8	**5**	Ph	Ph	*S*,*S*-Et-DuPhos	MeOH	0	-	-
9	**5**	Ph	Ph	*S*,*S*-Et-DuPhos	THF	100	-	-
10	**5**	Ph	$OC(CH_3)_3$	*R*,*R*-Et-DuPhos	MeOH	100	95	*R*[f]
11	**5**	Ph	$OC(CH_3)_3$	*S*,*S*-Et-DuPhos	MeOH	100	95	*S*[f]
12	**5**	Ph	OCH_2Ph	*S*,*S*-Et-DuPhos	MeOH	50	-	-
13	**5**	Ph	OCH_2Ph	*R*,*R*-Me-DuPhos	MeOH	100	79	*R*[g]
14	**5**	Ph	OCH_2Ph	*R*,*R*-Me-BPE	MeOH	100	78	*R*[g]
15	**5**	Ph	$OCH_2CH{=}CH_2$	*S*,*S*-Et-DuPhos	MeOH	0[d]	-	-
16	**5**	Ph	OCH_2Fm	*R*,*R*-Me-DuPhos	MeOH	90[e]	88	*R*[g]
17	**5**	Ph	OCH_2Fm	*S*,*S*-Me-DuPhos	MeOH	98	88	*S*[g]
18	**5**	Ph	OCH_2Fm	*R*,*R*-Et-DuPhos	MeOH	100	92	*R*[g]
19	**5**	Ph	OCH_2Fm	*S*,*S*-Et-DuPhos	MeOH	98	91	*S*[g]
20	**5**	$OC(CH_3)_3$	OCH_2Ph	*R*,*R*-Et-DuPhos	MeOH	20	-	-
21	**5**	*p*NO_2Ph	Me	*S*,*S*-Et-DuPhos	MeOH	50−75	95	-

[a] All hydrogenation substrates are methyl esters. Reactions were conducted at room temperature under an atmosphere of hydrogen (60−90 psi) for 15−60 h. [b] Isolated yields. [c] *N*-Benzoylalanine isolated (55% yield) with starting enamide. [d] Allyl carbamate protecting group was unstable under the hydrogenation conditions. [e] Dibenzofulvene identified as a reaction byproduct. [f] Assigned by HPLC analysis and comparison to an authentic sample of the product obtained from Hofmann rearrangement of L-asparagine. [g] Assigned by HPLC analysis after conversion of product to **6a**.

Scheme 2[a]



[a] Conditions: (a) DMFDMA or DMFDEA, $PhCH_3$, reflux; (b) NH_4OAc, MeOH, rt; (c) R″COCl or $(R''CO)_2O$, base, CH_2Cl_2/Et_2O.

acrylates (**3**) with excess ammonium acetate in methanol. Subsequent acylation of enamines (**4**) then gave the required hydrogenation substrates (**5**). In each case, only the *E*-isomer was isolated from the reaction mixture. Intramolecular hydrogen-bonding between the β-amide hydrogen and ester carbonyl group was evident in the ^{1}H NMR spectra of the enamides (**5**) where a significant downfield shift of the β-amide proton (δ 10−11) was observed. The α-*N*-benzoyl-β-*N*-acetyl-protected propenoate (**5a**) was chosen as our initial hydrogenation substrate, since both amine protecting groups were expected to be stable under the planned experimental conditions and would also allow UV-chromatographic monitoring of reaction progress.

Hydrogenation Study. To effect the hydrogenation of our prepared α,β-diamidopropenoates (**5**) we required a catalyst that operated under mild experimental conditions. The Rh-DuPhos catalysts, developed by Burk and co-workers,[1a] were chosen to achieve this end, since these catalysts facilitate highly selective hydrogenation of related α-enamides,[4] operate at low temperatures and hydrogen pressures and are commercially available. Attempted hydrogenation of *N*,*N*-dimethylenamine (**3**) and enamine (**4**) (entries 1 and 2, respectively) was unsuccessful, and only starting material was recovered (Table 1). This emphasizes the need to redirect electron density away from the C=C being reduced; acylation of the β-amino group therefore potentially serves two ends: it renders the olefin electron-poor and serves as a chelation site during hydrogenation. Interestingly, attempted hydrogenation of the hydrochloride salt of **4** (entry 3) resulted in deamination to give *N*-benzoylalanine. The enantiomeric excess of this reaction was not assessed.

Introduction of a second *N*-acyl group into the hydrogenation substrate provides two potential rhodium-chelation sites during reduction. Concern about whether these would behave in a matched or mismatched manner, however, was unwarranted. Et-DuPhos−Rh(I)-catalyzed hydrogenation of enamide (**5a**) (entries 6 and 7) in methanol under mild reaction conditions (60 psi H_2 pressure, room temperature) gave quantitative yields of

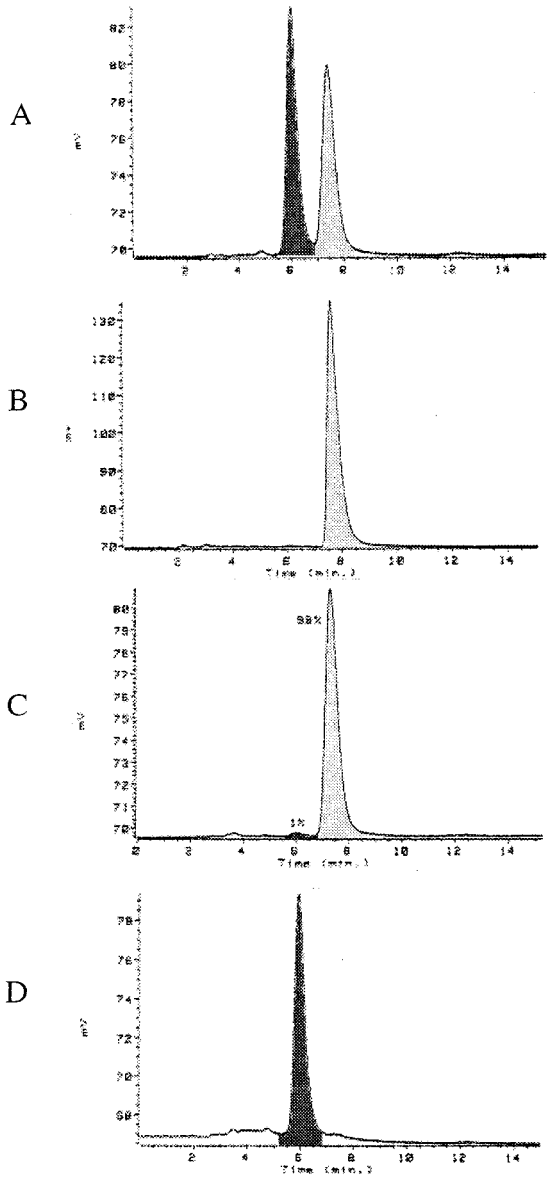


Figure 1. Chromatograms showing the separation of *R*- and *S*-α,β-diamidopropanoate (**6a**) using a chiral Daicel OJ HPLC column: (A) racemic **6a** generated by Pd/C-catalyzed hydrogenation of **5a**; (B) (*S*)-**6a** generated from L-asparagine; (C) crude product from [*S*,*S*]-Et-DuPhos-Rh(I)-catalyzed hydrogenation, 99% ee; and (D) crude product from [*R*,*R*]-Et-DuPhos-Rh(I)-catalyzed hydrogenation, 99% ee.

chiral diaminopropanoate (**6a**) in 99% ee.[15] Enantiomeric excess was determined by chiral HPLC and assignment of absolute configuration was facilitated through comparison of the reaction product with an authentic sample of (*S*)-**6a** obtained via Hofmann rearrangement of L-asparagine. Hydrogenation with the [*R*,*R*]-Et-DuPhos ligand afforded *R*-configured diaminopropanoate (**6a**); use of the antipode, [*S*,*S*]-Et-DuPhos, gave the enantiomeric *S*-isomer (Figure 1). Hydrogenation of (**5a**) with Rh−DIOP and Rh−BINAP catalysts under analogous reaction conditions resulted in only poor conversion (<5%) (entries 4 and 5). β-*N*-Carbamate-protected enamides also underwent quantitative and highly enantioselective reduction. Our studies showed that β-*N*-Boc-protected enamide esters could also be reduced with a similarly high enantiomeric excess of 95% (entries 10 and 11). To achieve complete reduction of β-*N*-Cbz-protected enamides, longer reaction times and less sterically demanding Me-DuPhos and Me-BPE phosphine ligands were employed (entries 12 and 14). Fmoc-protected enamide esters also underwent quantitative hydrogenation at 60 psi H_2 pressure over 48 h. The Et-DuPhos ligands resulted in slightly higher enantioselectivity (91−92% ee) compared with the Me-Duphos ligands (88% ee) (entries 16−19). Surprisingly, partial cleavage of the fluorenylmethyl carbamate group was observed in one reaction (entry 16) and this accounts for the lower than expected yield of diamidopropanoate (**6**). The allyl carbamate protecting group was found to be reactive under the hydrogenation conditions employed. Hydrogenation of the allyl group competed with enamide reduction to give a mixture of β-*N*-ethyloxycarbonylaminopropenoate (**5**) and β-*N*-ethyloxycarbonylaminopropanoate (**6**) (entry 15). α,β-Benzoylamino acrylate (**5**) (entry 8) failed to undergo hydrogenation with Rh-Et-DuPhos in methanol due to poor solubility. The expected diaminopropanoate (**6**) was obtained in excellent yield, however, using THF as the reaction solvent (entry 9).

The above study shows that the Rh-DuPhos catalyst can accommodate an increase in heteroatom substitution on the acrylate system provided that each amino group is first derivatized as its amide or carbamate. Importantly, the catalyst also tolerates changes to the electronic and steric properties of the β-*N*-acylamino protecting group and would therefore allow initial protection of this site with a group that would remain in the final target molecule. Despite this flexibility at the β-position, in our study so far we had examined only α-*N*-benzoyl-protected substrates. Although we found that this group could be removed without epimerization, strongly acidic conditions are required to achieve this end. To lend flexibility to the synthesis we turned our focus to the preparation and hydrogenation of α-*N*-carbamate-protected substrates to enable mild deprotection conditions to be employed. Synthesis of the required α-*N*-carbamate-protected enamide hydrogenation substrates, however, was hampered by very low yielding condensation reactions (<10%) between DMFDMA and α-*N*-Boc- and α-*N*-Cbz-protected glycines. Furthermore, all intermediates leading to the hydrogenation substrates bearing α-carbamate groups were unstable and difficult to handle. An alternative route to α-*N*-Boc-protected enamide esters (**5**) was eventually accomplished via a transprotection reaction developed by Burk and co-workers.[16] For example, *selective* transamidation of the α-benzoyl group of propenoate (**5a**) was achieved via reaction with di-*tert*-butyl dicarbonate followed by treatment with hydrazine hydrate. This strategy was not successful, however, in preparing the corresponding α-*N*-Cbz derivatives.

Hydrogenation of α-*N*-Boc-protected enamides proved to be very difficult. For example, hydrogenation of propenoate (**5**, R = Me, R′ = O^{t}Bu, R″ = OCH_2Ph) (entry 20) with Rh(I)−Et-DuPhos gave only a 20% conversion to the corresponding propanoate (**6**) after 15 h at elevated hydrogen pressure (90 psi). This result was surprising since related *N*-Cbz-protected enamide esters are reported to undergo smooth and highly enantioselective reduction with the Rh(I)−DuPhos catalyst.[4] In conclu-

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sion, the catalyst is considerably more sensitive to steric encumberment at the α-position of the enamide than at the *β*-position. This finding not only accounts for the prevalent use of *N*-acetyl-protected enamides in this field but also suggests that hydrogenation of the α,*β*-diamidopropenoate system is controlled via coordination through the α-*N*-acylamino group.

Mechanistic Study. The origin of the high enantioselection in the above hydrogenations merited further investigation. On the basis of literature precedent, we expected the formation of diastereromeric complexes upon chelation of the enamide substrate to the catalyst through normal symmetrical (μ^2) coordination of the C═C bond in addition to the oxygen atom of the amide carbonyl group.[17] Hence, *four* diastereomeric enamide−RhDuPhos complexes could be involved in the above transformations: The olefin can interact with either the *re* or *si* faces and coordinate through the α- or *β*-amide group. Due to the excellent selectivity demonstrated in the above hydrogenations, we believed that one diastereomer was playing a major role in the reduction. To investigate this postulate we synthesized ^{13}C-enriched analogues of the hydrogenation substrate (**5a**), α-*N*-[^{13}CO]-benzoylamino enamide (**7a**), and *β*-*N*-[^{13}CO]-acetylamino enamide (**7b**), via the synthetic pathway shown in Scheme 2.

The ^{31}P NMR spectrum of the commercially available [(COD)Rh(DuPhos)]OTf catalyst in d_4 methanol at room temperature displayed a doublet at *δ*70.9 (*J*148 (Rh−P)) (Figure 2). Hydrogenative removal of the COD ligand over 30−60 min at 90 psi H_2 generated the mononuclear [Rh(DuPhos)($CD_3OD)_2$]OTf species and resulted in a downfield shift of the phosphine doublet to *δ* 95.4 (*J* 205 (Rh−P)). Significantly, after addition of an equimolar amount of α-*N*-[^{13}CO]-benzoylamino enamide (**7a**) to the solvated catalyst at room temperature the NMR spectrum showed only *one* diastereomeric complex. Upon formation of the complex, the two phosphorus nuclei become inequivalent and two signals were observed at *δ* 88.8 (dd, *J* 166 (Rh−P_A), 34 (P_A−P_B)) and *δ* 82.5 (ddd, *J* 154 (Rh−P_B), 34 (P_A−P_B), 4 (P_B−^{13}C)). The additional splitting in the highfield signal suggested that the observed complex was arising through chelation of the α-amide carbonyl group.

This mode of chelation was further supported by the ^{13}C NMR spectrum of the diastereomeric complex. Unequivocal ^{13}C-assignment of the three carbonyl groups in the hydrogenation substrate was performed prior to the binding studies, and upon chelation to the rhodium cation, only the α-amido carbonyl signal was affected with a downfield shift from *δ* 169 to *δ* 182. This signal was also split into a doublet (*J* = 4 (^{13}C−P_B). The ester and *β*-acetyl groups on the other hand remained relatively uneffected by chelation (*δ* 167 → 168, 171.2 → 171.4, respectively) (Figure 3). ^{13}C and ^{31}P NMR binding studies with the *β*-*N*-[^{13}CO]-acetylamino enamide (**7b**) and solvated catalyst gave analogous spectra, now without the long range ^{13}C−^{31}P coupling between the highfield phosphorus nucleus and α-amide carbonyl. The importance of this chelation in the above hydrogenations was evident from studies performed on an α-*p*-nitrobenzoylamino derivative of **5a**. Under identical and more forceful experimental conditions, this substrate failed to reduce to completion and gave only a 50−75% yield of the α,*β*-diamidopropanoate (entry 21, Table 1). The electron-

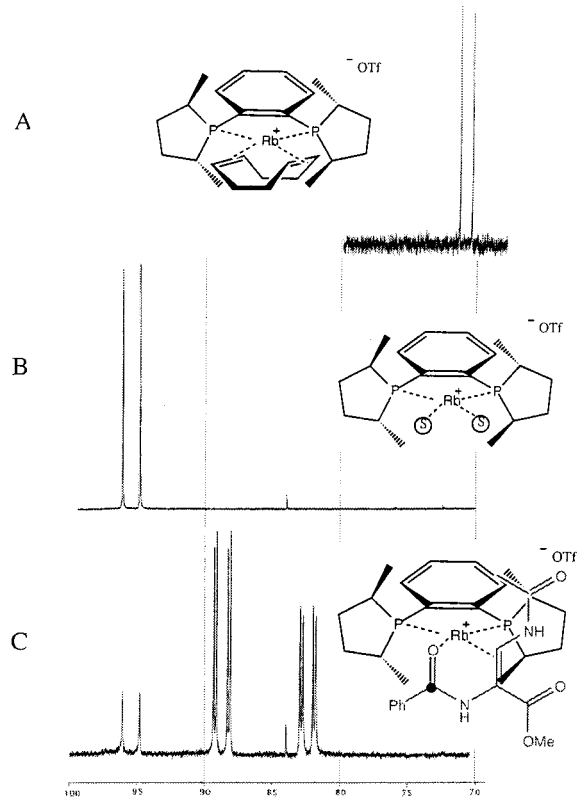

Figure 2. Hydrogenation sequence for Rh-DuPhos-catalyzed hydrogenation of α,*β*-diamidopropenoate (**7a**): ^{31}P NMR spectra of (A) [(COD)Rh(1,2-bis((2*R*,5*R*)-2,5-diethylphospholano)-benzene)]OTf in methanol-d_4; (B) methanol complex after exposure to hydrogen atmosphere; and (C) stable intermediate after the addition of ^{13}C-labeled enamide substrate (**7a**).

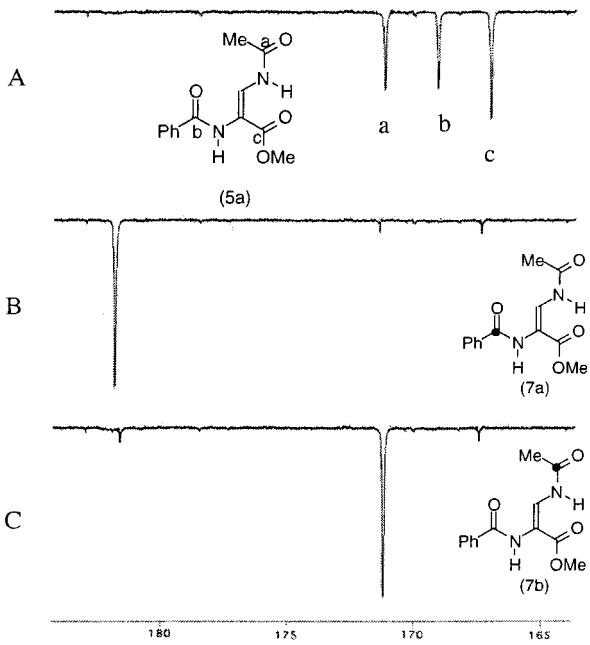

Figure 3. Carbonyl region of ^{13}C NMR spectra of carbon-13 enriched enamide in methanol-d_4: (A) unlabeled enamide (**5a**); (B) complex of **7a** with Rh-DuPhos catalyst; and (C) complex of **7b** with Rh-DuPhos catalyst.

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withdrawing effect of the nitro group not only affected chemical yield but also reduced enantioselectivity which dropped to 95% ee. From these studies, strong support for the coordinative involvement of the α-*amido group* has been obtained, and since hydrogenation with the [*R*,*R*]-DuPhos−Rh catalyst leads to (*R*)-configured products, coordination of the α-*si*-face of the enamide substrate must also occur during reduction. On the basis of molecular models and previous mechanistic studies,[18] it appears that the observed diastereomeric Rh−enamide complex does not correspond to the chirality of the product. Hence, hydrogenation must therefore be proceeding in an analogous fashion to that of bis(diarylphosphino)alkane-catalyzed hydrogenations of α-(acetamido)-cinnamates where the major enantiomeric product is produced from the less stable, minor diastereomeric complex.[17]

Conclusions

In summary, Rh(I)−DuPhos-catalyzed hydrogenation of α,β-diamidopropenoates provides a convenient and highly enantioselective route to chiral α,β-diaminopropanoic acid derivatives. Our studies strongly support the coordinative involvement of the α-amido group, as in simpler α-(*N*-acylamino)acrylate systems, during reduction. Changes to the electronic and steric properties of the α-*N*-acyl group were found to have a profound effect on hydrogenation yields but were well tolerated at the β-*N*-acyl position. We postulate that internal hydrogen bonding favors coordination through the α-amide group and renders the β-amide group unsuitably oriented for interaction with the rhodium cation. In our parallel studies on the simpler β-amino acid system, *E*-β-substituted-β-*N*-acylaminoacrylates were found to reduce in quantitative yields and high enantioselectivity with the Rh−DuPhos system. In the corresponding *Z*-series, however, where internal hydrogen bonding is evident, no reduction is observed under mild operating conditions, and forcing conditions are required for reduction to the detriment of enantioselectivity.[19] This does not wholly account for the excellent selectivity described herein since Rh−DuPhos-catalyzed hydrogenation of α-substituted-β-*N*-acylaminoacrylates does not display the same geometric-isomer bias.[20] Future work will explore the scope of Rh−phosphine catalysis to reduce enamides of increasing complexity with a view to β-lactam synthesis.

Experimental Section

General Procedures. Melting points were determined using a hot-stage melting point apparatus and are uncorrected. Infrared spectra were recorded on a FT-IR spectrophotometer as potassium bromide disks of solids (KBr) or as thin films of liquids (neat) between sodium chloride plates. Nuclear magnetic resonance spectra (^{1}H, ^{31}P, and ^{13}C NMR) were recorded with 200, 300, or 400 MHz spectrometers. Electron impact ionization (EI) spectra (*m*/*z*) were recorded on a mass spectrometer operating at 200 °C/70 eV. Analytical thin-layer chromatography (TLC) was performed on plastic or glass slides coated with silica gel (Polygram SIL G/UV$_{254}$). Column chromatography was performed using Merck silica gel 60, 0.063−0.200 mm (70−230 mesh). Degassed methanol (HPLC grade) was used in all hydrogenation reactions.

DMFDMA refers to *N*,*N*-dimethylformamide dimethyl acetal and was used as supplied. Carbon-13-labeled Ba^{13}CO$_3$ (90%) was used to prepare benzoyl-*carbonyl*-^{13}C-chloride[21] for the synthesis of *N*-benzoyl-*carbonyl*-^{13}C-glycine.[22] Acetyl-1-^{13}C chloride was distilled prior to use. Deuterated methanol was used as supplied and degassed via three freeze−thaw cycles on a high vacuum line prior to NMR studies. All hydrogenation catalysts were used as received from the suppliers. In all Rh−phosphine hydrogenations, high purity (<10 ppm) hydrogen and nitrogen were used and purified by passage through water, oxygen, and hydrocarbon traps. The enantiomeric excess of the hydrogenation products was determined via chiral HPLC analysis using a Diacel Chiracel OJ column. For the NMR-hydrogenation studies, all procedures were performed under a dry and inert atmosphere of nitrogen using modified Schlenk techniques.

Preparation of Hydrogenation Substrates

Methyl 2-*N*-Benzoylamino-3-amino-2-propenoate (4, R = Me, R′ = Ph). Ammonium acetate (6.92 g, 89.8 mmol) was added to a solution of the tertiary amine (**3**, R = Me, R′ = Ph) (2.22 g, 8.93 mmol) in ethanol (100 mL), and the resulting mixture was stirred overnight at room temperature. The reaction mixture was then evaporated to dryness under reduced pressure. The resulting white precipitate was treated with a 10% sodium bicarbonate solution (100 mL) and diluted with dichloromethane (80 mL). The phases were separated, and the aqueous phase was diluted with saturated sodium chloride solution (50 mL) and further extracted with dichloromethane (2 × 40 mL). The organic extracts were combined, washed with saturated sodium chloride solution (2 × 50 mL), dried (MgSO$_4$), and evaporated under reduced pressure to give the primary enamine (**4**, R = Me, R′ = Ph) as a colorless precipitate (1.66 g, 84%), mp 148−150 °C. (HRMS: Found: M + H$^+$, 221.0910. $C_{11}H_{13}N_2O_3$ requires 221.0926). ν_{max} (KBr): 3406s, 1676m, 1655s, 1637s cm^{-1}. ^{1}H NMR (200 MHz, CDCl$_3$): δ 3.76 (s, 3H), 5.10−5.40 (m, 2H), 7.42−7.54 (m, 4H), 7.80−7.91 (m, 3H). ^{13}C NMR (75 MHz, CDCl$_3$): δ 51.8, 101.1, 127.3, 128.4, 131.8, 134.0, 137.0, 164.7, 166.5. Mass spectrum (ESI+, MeOH): *m*/*z* 243.1 ([M + Na]$^+$); 221.2 ([M + H]$^+$). The isolated enamine (**4**) was used without further purification and stored at 0 °C to avoid decomposition.

Methyl 2-*N*-[^{13}CO]-Benzoylamino-3-amino-2-propenoate (4*, R = Me, R′ = Ph). Ammonium acetate (1.44 g, 18.7 mmol) was added to a solution of methyl 2-*N*-[^{13}CO]-benzoylamino-3-*N*,*N*-(dimethylamino)-2-propenoate (**3**) (0.46 g, 1.87 mmol) in methanol (35 mL), and the mixture was stirred at room temperature. After 15 h, the solvent was removed under reduced pressure. The resulting precipitate was treated with a 10% sodium bicarbonate solution (45 mL), and the mixture was then extracted into dichloromethane (3 × 10 mL). The aqueous phase was further diluted with saturated sodium chloride solution (25 mL) and extracted with dichloromethane (2 × 25 mL). The combined organic extract was then washed with saturated sodium chloride solution (35 mL), dried (MgSO$_4$), and evaporated under reduced pressure to give the ^{13}C-labeled primary enamine (**4***, R = Me, R′ = Ph) (0.37 g, 89%) as a colorless solid, mp 152−154 °C. ν_{max} (KBr): 3410s, 1676m, 1654m, 1633m cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ 3.78 (s, 3H), 5.10−5.30 (m, 2H), 7.40−7.58 (m, 4H), 7.84−7.91 (m, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 52.3, 127.4 (d, *J* 16.9 Hz), 128.6 (d, *J* 21.1 Hz), 131.8, 134.1 (d, *J* 65.0 Hz), 165.4, 166.5; C2 and C3 were not observed. Mass spectrum (ESI+, MeOH): *m*/*z* 244.0763 ([M + Na]$^+$). $^{12}C_{10}{}^{13}C_1H_{12}N_2O_3Na$ requires 244.0779. The isolated enamine (**4***) was used without further purification and stored at 0 °C to avoid decomposition.

Methyl 2-*N*-Benzoylamino-3-*N*-acetylamino-2-propenoate (5a, R = Me, R′ = Ph). Distilled acetyl chloride (0.20 mL, 2.81 mmol) in dichloromethane (5 mL) was added drop-

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wise to a stirred and ice-cooled solution of methyl 2-*N*-benzoylamino-3-amino-2-propenoate (**4**) (0.52 g, 2.34 mmol) and pyridine (0.23 mL, 2.81 mmol) in dichloromethane (14 mL) and diethyl ether (7 mL). After complete addition, the reaction mixture was warmed to room temperature, and reaction progress was monitored at 30 min intervals by TLC (SiO_2, petroleum ether:ethyl acetate; 1:1). After 1.5 h, TLC showed the absence of starting primary amine, and the reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (2 × 8 mL). The combined organic extract was washed with saturated sodium chloride solution (5 mL), dried ($MgSO_4$), and evaporated under reduced pressure to a yellow solid. Purification by column chromatography (SiO_2, light petroleum:ethyl acetate; 1:1) gave the title enamide as an off-white solid (0.64 g, 90%), mp 118−120 °C. Microanalysis: Found, C 59.51%, H 5.37%, N 10.68%; $C_{13}H_{14}N_2O_4$ requires C 59.54%, H 5.38%, N 10.68%. ν_{max} (KBr): 3449s, 1702m cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20 (s, 3H, $COCH_3$), 3.85 (s, 3H, $COOCH_3$), 7.50 (t, *J* 7.8 Hz, 2H, H3′, 5′), 7.59 (t, *J* 7.5 Hz, 1H, H4′), 7.81−7.89 (m, 3H, H2′, 6′, C=CH), 8.45 (bs, 1H, N*H*COPh), 10.41 (d, *J* 10.1 Hz, 1H, N*H*$COCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.8 (CO*C*H_3), 52.9 (O*C*H_3), 108.3 (C2), 122.0 (C3), 127.3 (C3′, 5′), 128.9 (C2′, 6′), 132.5 (C4′), 133.2 (C1′), 165.9 (COPh), 166.2 (C1), 168.0 (*C*OCH_3). ^{1}H NMR (300 MHz, CD_3OD): δ 2.10 (s, 3H, $COCH_3$), 3.77 (s, 3H, OCH_3), 7.49 (t, *J* 7.5 Hz, 2H, H3′, 5′), 7.58 (t, *J* 7.2 Hz, 1H, H4′), 7.96 (d, *J* 6.8 Hz, 2H, H2′, 6′), 8.06 (s, 1H, C=CH). ^{13}C NMR (75 MHz, CD_3OD): δ 22.8 (CO*C*H_3), 52.6 (O*C*H_3), 109.7 (C2), 128.8 (C3′, 5′), 129.4 (C2′, 6′), 131.4 (C3), 133.0 (C4′), 134.8 (C1′), 167.0 (C1), 169.1 (Ph*C*O), 171.2 (*C*OCH_3). Mass spectrum (ESI+, MeOH): *m*/*z* 285.1 ([M + Na]$^+$), 263.1 ([M + H]$^+$).

Methyl 2-*N*-Benzoylamino-3-*N*-[^{13}CO]-acetylamino-2-propenoate (7b, R = Me, R′ = Ph, R″ = Me). Pyridine (0.31 mL, 3.78 mmol) was added to a solution of methyl 2-*N*-benzoylamino-3-amino-2-propenoate (**4**) (0.69 g, 3.15 mmol) in dichloromethane (14 mL) and diethyl ether (7 mL). The mixture was cooled to 0 °C, and a solution of acetyl-^{13}C-chloride (0.25 g, 3.15 mmol) in dichloromethane (2 mL) was then added. The reaction mixture was allowed to rise to room temperature over 10 min, and the reaction progress was monitored at 30 min interval by TLC (SiO_2, petroleum ether:ethyl acetate; 1:1). After 3.5 h, TLC showed the absence of starting primary amine, and the reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (2 × 10 mL). The combined organic extract was washed with dilute (2 M) hydrochloric acid (20 mL) and saturated sodium chloride solution (5 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give a yellow solid (0.75 g). Purification by column chromatography (SiO_2, light petroleum:ethyl acetate; 1:1) gave the title ^{13}C-labeled enamide (**7b**) (0.42 g, 51%) as a fine white solid, mp 116−118 °C. ν_{max} (KBr): 3413s, 1686m cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.24 (d, *J* 6.3 Hz, 3H, $^{13}COCH_3$), 3.89 (s, 3H, $COOCH_3$), 7.54 (t, *J* 7.6 Hz, 2H, H3′, 5′), 7.62 (t, *J* 7.3 Hz, 1H, H4′), 7.90−8.00 (m, 3H, H2′, 6′, C=CH), 8.48 (bs, 1H, PhCON*H*), 10.44−10.52 (m, 1H, N*H*$COCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.8 (d, *J* 52.8 Hz, ^{13}CO*C*H_3), 52.9 (COO*C*H_3), 108.4 (d, *J* 5.0 Hz, C2), 122.0 (C3), 127.3 (C3′, 5′), 129.0 (C2′, 6′), 132.6 (C4′), 133.3 (C1′), 166.0 (*C*OPh), 166.3 (*C*OCH_3), 167.9 (^{13}*C*OCH_3). ^{1}H NMR (300 MHz, CD_3OD): δ 2.10 (d, *J* 6.6 Hz, 3H, $COCH_3$), 3.76 (s, 3H, OCH_3), 7.49 (t, *J* 7.5 Hz, 2H, H3′, 5′), 7.58 (t, *J* 7.2 Hz, 1H, H4′), 7.97 (d, *J* 6.9 Hz, 2H, H2′, 6′), 8.06 (d, *J* 3.0 Hz, 1H, C=CH). ^{13}C NMR (75 MHz, CD_3OD): δ 23.5 (d, *J* 50.9 Hz, CO*C*H_3), 52.6 (OCH_3), 109.7 (d, *J* 4.3 Hz, C2), 128.8 (C3′, 5′), 129.4 (C2′, 6′), 131.4 (C3), 133.0 (C4′), 134.8 (C1′), 167.0 ($COOCH_3$), 169.1 (PhCO), 171.2 (^{13}*C*OCH_3). Mass spectrum (ESI+, MeOH): *m*/*z* 286.0870 ([M + Na]$^+$). $^{12}C_{12}{}^{13}C_1H_{14}N_2O_4Na$ requires 286.0885.

Methyl 2-*N*-[^{13}CO]-Benzoylamino-3-*N*-acetylamino-2-propenoate (7a, R = Me, R′ = Ph, R″ = Me). Pyridine (0.14 mL, 1.71 mmol) was added to a solution of methyl 2-*N*-[^{13}CO]-benzoylamino-3-amino-2-propenoate (4*) (0.31 g, 1.42 mmol) in dichloromethane (14 mL) and diethyl ether (7 mL). The mixture was then cooled to 0 °C. Distilled acetyl chloride (0.12 mL, 1.71 mmol) in dichloromethane (5 mL) was added dropwise to the reaction mixture. After complete addition, the reaction mixture was allowed to warm to room temperature, and reaction progress was monitored at 30 min intervals by TLC (SiO_2, petroleum ether:ethyl acetate; 1:1). After 2.5 h, TLC showed the absence of starting primary amine (**4***), and the reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (2 × 8 mL). The combined organic extract was washed with dilute (2 M) hydrochloric acid solution (15 mL) and saturated sodium chloride solution (15 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give the title ^{13}C-labeled enamide (**7a**) as a colorless solid (0.28 g, 73%), mp 117−120 °C. ν_{max} (KBr): 3416s, 1722w, 1696m, 1655s cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.20 (s, 3H, $COCH_3$), 3.84 (s, 3H, $COOCH_3$), 7.51 (t, *J* 7.5 Hz, 2H, H3′, 5′), 7.60 (t, *J* 7.2 Hz, 1H, H4′), 7.85−7.90 (m, 3H, H2′, 6′, C=CH), 8.44 (s, 1H, Ph^{13}CON*H*), 10.42 (d, *J* 9.9 Hz, 1H, N*H*-$COCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.8 (CO*C*H_3), 52.9 (COO*C*H_3), 108.4 (C2), 122.1 (C3), 127.3 (d, *J* 2.3 Hz, C3′,5′), 129.0 (d, *J* 4.24 Hz, C2′,6′), 132.6 (C4′), 133.3 (d, *J* 66.0 Hz, C1′), 165.9 (Ph^{13}*C*O), 166.3 (*C*$OOCH_3$), 167.9 (*C*OCH_3). ^{1}H NMR (300 MHz, CD_3OD): δ 2.10 (s, 3H, $COCH_3$), 3.77 (s, 3H, OCH_3), 7.50 (t, *J* 7.8 Hz, 2H, H3′, 5′), 7.58 (t, *J* 7.2 Hz, 1H, H4′), 7.95−8.00 (m, 2H, H2′, 6′), 8.06 (s, 1H, C=CH). ^{13}C NMR (75 MHz, CD_3OD): δ 22.8 (CO*C*H_3), 52.6 (OCH_3), 109.7 (C2), 128.8 (d, *J* 2.6 Hz, C3′, 5′), 129.3 (d, *J* 4.3 Hz, C2′, 6′), 131.4 (C3), 133.0 (C4′), 134.9 (d, *J* 64.9 Hz, C1′); 167.0 (C1), 169.1 (Ph^{13}*C*O), 171.2 (*C*OCH_3). Mass spectrum (ESI+, MeOH): *m*/*z* 286.0884 ([M + Na]$^+$]. $^{12}C_{12}{}^{13}C_1H_{14}N_2O_4Na$ requires 286.0885.

Hydrogenation Study

General Hydrogenation Procedure. In a drybox, a Fisher-Porter tube was charged with catalyst (1 mg), deoxygenated solvent (~5 mL), and substrate (30−200 mg). Three vacuum/N_2 cycles to purge the gas line of any oxygen followed by three vacuum/N_2 cycles of the vessel were carried out before the tube was pressurized with hydrogen to the required pressure (psi). The reaction was then stirred at room temperature for the specified period of time. The pressure in the vessel was then released and the contents were evaporated under reduced pressure to dryness. The crude product (**6**) was passed through a short plug of silica prior to spectroscopic and chromatographic analysis. Hydrogenation experiments are described using the following format: substrate, solvent, catalyst, hydrogen pressure, reaction time, isolated yield, enantiomeric excess (assigned configuration), retention time (HPLC conditions).

(2*S*)-Methyl 2-*N*-Benzoylamino-3-*N*-acetylaminopropanoate. (a) [Methyl 2-*N*-benzoylamino-3-*N*-acetylamino-2-propenoate (110 mg), methanol, [(COD)Rh((*S*,*S*)-Et-DuPHOS)]-OTf, 60 psi H_2, 15 h; 100% yield, 99.0% ee (*S*), t_1 = 7.5 min (Chiralcel OJ, ambient temperature, flow rate = 1.0 mL/min, detection at 250 nm, eluent = 20% IPA:80% hexane)]. (b) [Methyl 2-*N*-benzoylamino-3-*N*-acetylamino-2-propenoate (50 mg), methanol, [(COD)Rh((*S*,*S*)-Me-DuPHOS)]OTf, 60 psi H_2, 60 h; 100% yield, 79.9% ee (*S*), t_1 = 7.5 min].

6a (R, R″ = Me, R′ = Ph): Colorless solid: $[\alpha]^{25}_D$ −1.30° (*c* 1.00, MeOH). Microanalysis: Found, C 59.06%, H 5.99%, N 10.60%; $C_{13}H_{16}N_2O_4$ requires C 59.08%, H 6.10%, N 10.60%. ν_{max} (KBr): 3556m, 3478s, 3414s, 1736m, 1650m cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.00 (s, 3H), 3.75 (t, *J* 5.7 Hz, 2H), 3.77 (s, 3H), 4.77 (q, *J* 5.7 Hz, 1H), 6.58 (bs, 1H), 7.43 (t, *J* 6.9 Hz, 2H), 7.51 (t, *J* 6.0 Hz, 1H), 7.84 (d, *J* 7.2 Hz, 2H), 7.90 (d, *J* 6.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.1, 41.6, 52.8, 54.7, 127.1, 128.5, 131.8, 133.0, 167.4, 170.5, 172.2. Mass spectrum (ESI+, MeOH): *m*/*z* 265.1, ([M + H]$^+$), 287.1 ([M + Na]$^+$). Accurate mass spectrum (ESI+, MeOH): *m*/*z* 265.1184 ([M + H]$^+$), $C_{13}H_{17}N_2O_4$ requires 265.1188.

(2*R*)-Methyl 2-*N*-Benzoylamino-3-*N*-acetylaminopropanoate. [Methyl 2-*N*-benzoylamino-3-*N*-acetylamino-2-propenoate (62 mg), methanol, [(COD)Rh((*R*,*R*)-Et-DuPHOS)]OTf, 60 psi H_2, 15 h; 100% yield, 99.1% ee (*R*), t_2 = 6 min (Chiralcel OJ, ambient temperature, flow rate = 1.0 mL/min, detection at 250 nm, eluent = 20% IPA:80% hexane)].

6a: Colorless solid: $[\alpha]^{25}_D$ +1.32° (*c* 2.12, MeOH).

Mechanistic Study: ^{31}P and ^{13}C NMR Binding Studies between [*R*,*R*]-Ethyl-DuPHOS−Rh(I) and ^{13}C-Labeled Substrates (7a and 7b)

^{31}P NMR of [(1,5-Cyclooctadiene)Rh(I)(1,2-bis((2*R*,5*R*)-2,5-diethylphosphalano)benzene)] Triflate in CD_3OD. In a drybox, the catalyst [(COD)Rh((*R*,*R*)-Et-DuPHOS)]OTf (ca. 3 mg) was dissolved in degassed deuterated methanol to form a yellow solution. The resulting solution was transferred under an atmosphere of argon into a 5 mm NMR tube. The tube was then reversibly sealed with a screw-cap Teflon seal, and ^{31}P NMR spectra (162 MHz, CD_3OD) were recorded at different temperatures.

^{31}P NMR (25 °C): δ 70.9 (d, *J* 148.3 Hz); ^{31}P NMR (−30 °C): δ 70.9 (d, *J* 148.3 Hz); ^{31}P NMR (−60 °C): δ 70.9 (d, *J* 148.3 Hz), 71.8; 31P NMR (−80 °C): δ 70.9 (d, *J* 148.3 Hz), 71.8; ^{31}P NMR (−80 °C → 25 °C): δ 70.9 (d, *J* 148.3 Hz.

^{31}P NMR of [Rh(1,2-bis((2*R*,5*R*)-2,5-diethylphosphalano)benzene)] Triflate ("solvated catalyst") in CD_3OD. [(COD)Rh((*R*,*R*)-Et-DuPHOS)]OTf (ca. 5 mg) was dissolved in degassed methanol-d_4 (CD_3OD). The bright yellow solution was exposed to a hydrogen atmosphere (90 psi) at room temperature. After 1 h, a dark brown solution had formed. The ^{31}P spectrum was then recorded: ^{31}P NMR (162 MHz, CD_3OD, 25 °C): δ 84.0 (minor); δ 95.4 (d, *J* 205.3 Hz). In a separate experiment, hydrogenation of the catalyst over a 20 min period at 60 psi pressure of hydrogen was found to be incomplete.

^{31}P and ^{13}C NMR of the Solvated Catalyst with Labeled Substrate (7a). Under an atmosphere of argon, [(COD)Rh((*R*,*R*)-Et-DuPHOS)]OTf (50.0 mg, 69.1 μmol) was dissolved in deuterated methanol (1.5 mL) to form a bright yellow solution. Hydrogen gas was added to the stirred solution at a pressure of 90 psi. After 1 h, a dark brown solution had formed. The solution was transferred to a 5 mm NMR tube under an atmosphere of argon and the α-labeled substrate, methyl 2-*N*-[^{13}CO]-benzoylamino-3-*N*-acetylamino-2-propenoate (**7a**) (18.2 mg, 69.1 μmol), was added. ^{31}P and ^{13}C NMR spectra were then recorded: ^{31}P NMR (162 MHz, CD_3OD): δ 95.4 (d, *J* 205.3 Hz (Rh−P), unbound catalyst), 88.8 (dd, *J* 165.9 Hz (Rh−P), 33.7 Hz (P_1-P_2)), 82.5 (ddd, *J* 153.7 Hz (Rh−P), 33.7 Hz (P_1-P_2), 3.5 Hz ($P_1-{}^{13}C$)). ^{13}C NMR (100 MHz, CD_3OD, 25 °C): shows bound and unbound enamide (**7a**). Unbound substrate: δ 109.8 (C2), 129.0 (d, *J* 2.2 Hz, C3′, 5′), 129.5 (d, *J* 4.4 Hz, C2′, 6′), 131.6 (C3), 133.1 (C4′), 167.2 (*C*OOCH$_3$), 169.3 (Ph^{13}*C*O), 171.3 (*C*OCH$_3$), C1′ not observed. Bound substrate: δ 76.6 (d, *J* 20.1 Hz (Rh−C), C2), 90.6 (d, *J* 12.1 Hz (Rh−C), C3), 129.7 (d, *J* 2.3 Hz, C3′, 5′), 130.0 (d, *J* 4.4 Hz, C2′,6′), 134.8 (C4′), 168.3 (*C*OOCH$_3$), 171.4 (*C*OCH$_3$), 181.8 (d, *J* 3.5 Hz, Ph^{13}*C*O).

^{31}P and ^{13}C NMR of the Solvated Catalyst with the Labeled Substrate (7b). Under an atmosphere of argon, [(COD)Rh((*R*,*R*)-Et-DuPHOS)]OTf (47.8 mg, 66.2 μmol) was dissolved in deuterated methanol (1.5 mL) to form a bright yellow solution. Hydrogen gas was added to the stirred solution at a pressure of 90 psi. After 1 h, a dark brown solution had formed. The solution was transferred to a 5 mm NMR tube under an atmosphere of argon, and the labeled substrate, methyl 2-*N*-benzoylamino-3-*N*-[13CO]-acetylamino-2-propenoate (**7b**) (17.4 mg, 66.2 μmol), was added. ^{31}P and ^{13}C NMR spectra were then recorded:

^{31}P NMR (162 MHz, CD_3OD, 25 °C): δ 95.4 (d, *J* 205.3 Hz (Rh−P), unbound catalyst), 88.7 (dd, *J* 165.9 Hz (Rh−P)), 34.0 Hz (P_1-P_2)), 82.4 (dd, *J* 153.6 Hz (Rh−P)), 33.9 Hz (P_1-P_2)). ^{13}C NMR (100 MHz, CD_3OD, 25 °C): shows bound and unbound enamide (**7b**). Unbound substrate: δ 109.8 (C2), 129.0 (C3′, 5′), 129.5 (C2′, 6′), 131.6 (C3), 133.1 (C4′), 134.9 (C1′), 167.2 (*C*OOCH$_3$), 169.3 (Ph*C*O), 171.3 (^{13}COCH$_3$). Bound substrate: δ 76.7 (d, *J* 21.3 Hz, C2), 90.6 (d, *J*12.4 Hz, C3), 129.7 (C3′,5′), 130.0 (C2′, 6′), 130.6 (C1′), 134.8 (C4′), 168.3 (*C*OOCH$_3$), 171.4 (^{13}COCH$_3$), 181.8 (PhCO).

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Note Added after ASAP Posting. The version of this paper posted on January 13, 2001, had incorrect author attributions and was withdrawn from the Web on January 31, 2001. The version with full authorship and affiliations was posted on May 22, 2001.

Supporting Information Available: Experimental procedures and spectral data for compounds **3**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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