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Enantioselective Synthesis of β-Amino Acids Based on BINAP—Ruthenium(II) Catalyzed Hydrogenation

William D. Lubell, Masato Kitamura, and Ryoji Noyori*

Department of Chemistry, Nagoya University, Chikusa, Nagoya 464-01, Japan

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Abstract: BINAP—Ru(II) catalyzed hydrogenation of β-substituted (*E*)-β-(acylamino)acrylic acids allows efficient enantioselective synthesis of β-amino acids. The *Z* double bond isomers which possess an intramolecular hydrogen bond between amide and ester groups are more reactive but are hydrogenated with poor enantioselectivity. BINAP—Rh(I) complexes afford only moderate stereoselectivity with the opposite sense of enantioselection.

β-Amino acids are important natural products found in biologically active peptides[1] as well as useful chiral building blocks in the synthesis of β-lactam antibiotics.[2] Substitution of β-amino acids for α-amino acids in biologically active peptides has also been used in recent efforts to prepare peptide analogues with increased potency and enzymatic stability.[3] For these reasons the enantioselective synthesis of β-amino acids has attracted considerable interest. Several diastereoselective syntheses of β-amino acids have been reported in which chiral auxiliaries attached to either the amino or carboxylate group have been employed to achieve stereoselectivity. These include: Michael addition of amines and lithium amides to α,β-unsaturated esters;[4] hydrogenation of enamido esters;[5] condensation of Schiff bases with Reformatsky reagents;[6] cycloaddition of Schiff bases with ketenes;[7] alkylation of Ti(IV) enolates;[8] and Pd catalyzed addition of aryl iodides to a dihydropyrimidone.[9] Transformation of optically pure α-amino acids has also been employed to synthesize β-amino acids.[10,11] In all these examples the stoicheometric use of a chiral (non-racemic) source has limited the utility of these methods for large-scale preparation of β-amino acids. Enantioselective hydrogenation of prochiral 3-amino acrylic acid derivatives in the presence of a chiral catalyst offers the simplest solution to this problem; however, previous efforts in this endeavor have had only modest success giving the products in only 2.6—78% enantiomeric excess (ee).[12]

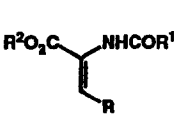
We have previously demonstrated that BINAP-transition metal complexes [BINAP = 2,2'-bis(diarylphosphino)-1,1'-binaphthyl] serve as excellent catalysts for enantioselective hydrogenation of enamide substrates.[13] For example, hydrogenation of α-(acylamino)acrylic acids of type **1** leads to natural and unnatural α-amino acid derivatives of high enantiomeric purity.[14,15] Similarly, hydrogenation of olefinic substrates of type **2** and **3** allows for general asymmetric syntheses of isoquinoline alkaloids as well as morphines, benzomorphans, and morphinans.[16,17] Several notable characteristics are present in these asymmetric reactions. Enantioselective hydrogenation of **1** (R = phenyl) is achieved with both BINAP—Rh(I) and —Ru(II) complexes with the rhodium catalysts acting somewhat better. Rhodium catalyzed hydrogenation of the *Z* isomer of **1** (R = phenyl) generates α-amino acid derivatives with absolute configuration at C-1 opposite to that obtained from hydrogenation of the *E* isomer. Ruthenium complexes show much higher enantioselectivity in the hydrogenation of substrates **2** and **3**, and only *Z* olefinic substrates are reduced. Ruthenium and rhodium catalysts with the same BINAP chirality predominantly produce opposite enantiomers from hydrogenation of

substrates **1** (R = phenyl) and **2** (R = substituted phenyl). The high enantioselectivity obtained from hydrogenation of enamide substrates **1**, **2** and **3** with BINAP transition metal complexes prompted us to examine reduction of the structurally related enamido esters (*Z*)-**4** and (*E*)-**4**, in hope to efficiently prepare β-amino acid derivatives **5** with high enantiomeric purity.

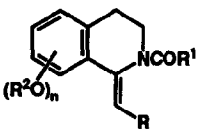
Substrates and Products

Hydrogenation substrates **4** were prepared from methyl β-amino acrylates **6**. Methyl 3-acetamido-2-butenoate (**4a**) was synthesized by acylation of commercially available β-amino crotonate (**6a**) with acetic anhydride and pyridine in THF at reflux. This provided a mixture that was separated on chromatography and contained both (*E*)- and (*Z*)-enamide esters **4a** in a 1:1.6 ratio, contaminated with β-keto ester **7a** from acylation on carbon instead of nitrogen. Structural assignments of double bond isomers **4** were made based on NOE difference spectroscopy which showed a significant nuclear Overhauser effect between the vinyl and allylic protons for only the *Z* isomers.[18] Amide proton resonances of *Z* isomers **4** are strongly shifted downfield in the proton NMR spectra due to hydrogen bonding with the ester carbonyl.[19] Pure (*E*)-enamido ester (*E*)-**4a** was also obtained on exposure of (*Z*)-**4a** in toluene to light from a Hg lamp for 100 h which produced a 3:1 mixture of *Z* and *E* isomers from which (*E*)-**4a** crystallized and was removed by filtration. Methyl 3-acetamido-5-methyl-2-hexenoate (**4b**) was prepared from Meldrum's acid.[20] Acylation with isovaleryl chloride and pyridine as base in dichloromethane followed by methanolic hydrolysis provided methyl 3-oxo-5-methylhexanoate, which on treatment with ammonium acetate in methanol was converted to methyl 3-amino-5-methyl-2-hexenoate (**6b**). Treatment of this enamino ester with acetic anhydride and pyridine under our standard conditions provided a separable mixture containing (*E*)- and (*Z*)-methyl 3-acetamido-5-methyl-2-hexenoates (**4b**) along with β-keto ester **7b** from acylation on carbon. Methyl β-amidocinnamate **4c** was synthesized from ethyl benzoylacetate which was trans-esterified in methanolic HCl and subsequently converted to methyl β-aminocinnamate on treatment with ammonium acetate in methanol. Acylation of the amine with acetic anhydride and pyridine in refluxing THF provided the desired methyl β-acetamidocinnamate (**4c**) as a 1.4:1 mixture of the *Z* and *E* stereoisomers that were separated on chromatography. Alkylation of either (*Z*)- or (*E*)-enamido ester **4c** with methyl iodide in THF with sodium hydride as base selectively produced (*E*)-*N*-methylenamido ester (*E*)-**9** in good yield. (*Z*)-*N*-Methylenamido ester (*Z*)-**9** was obtained by photochemical isomerization of (*E*)-**9** in chloroform with light from a Hg lamp which after 100 h produced a 3:2 *E*:*Z* mixture that was separated by chromatography.

Hydrogenation products, amido esters (*R*)- and (*S*)-**5** were directly convertible to β-amino acid **8** on treatment with 6 N HCl. To ascertain the extent of asymmetric induction in the hydrogenation, β-amido ester **5** was reduced with excess $LiAlH_4$ in THF at reflux for 2 h to furnish 3-ethylamino alcohols **11** which on treatment with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (GITC) in CH_3CN gave diastereomeric tetraacetylglucose thioureas that were analyzed on reversed phase HPLC.[21] For comparison purposes β-amido ester **5a** was also selectively hydrolyzed with LiOH to 3-acetamidobutanoic acid which was coupled via its acid chloride to α-methylnaphthylamine and analyzed with ^1H NMR spectroscopy in which the α-methyl doublets of the diastereomeric amides were clearly resolved.[22] The enantiomeric purity of *N*-methylacetamido ester **10** was ascertained by conversion to 3-methylamino-3-phenyl-1-propanol (**12**) which was coupled to GITC and analyzed on HPLC. Methylamino alcohol **12** was produced by selective reduction of the ester group of **10** with $LiAlH_4$ in THF at –78 °C, followed by acid hydrolysis of the amide.



1, R = H, aryl



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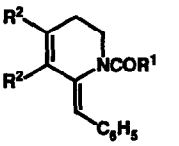

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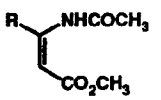
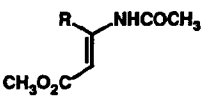
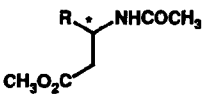


(*Z*) -4



(*E*) -4



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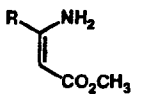

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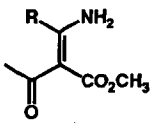

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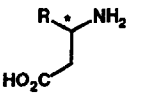

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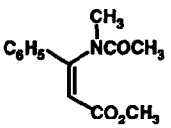
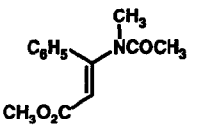
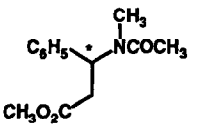


(*Z*) -9



(*E*) -9



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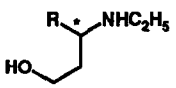

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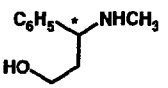

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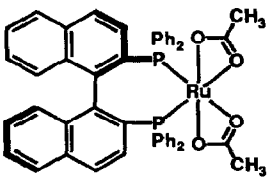
a: R = CH_3
b: R = $(CH_3)_2CHCH_2$
c: R = C_6H_5

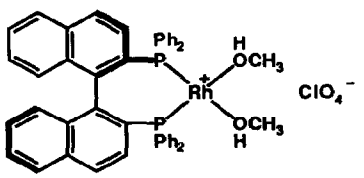
Hydrogenation

We first examined hydrogenation of **4** using the BINAP—Ru(II) diacetate complex **13**. The results are summarized in Table I. When hydrogenation of (*Z*)-**4a** was conducted in methanol containing 0.5 mol % of (*R*)-**13** at room temperature under 4 atm of hydrogen, β-amido ester **5a** was obtained in only 5% ee. Fortunately, however, hydrogenation of the *E* stereoisomer (*E*)-**4a** with the same catalyst at 4 atm of hydrogen formed (*S*)-**5a** in 92% ee in quantitative yield. This result represented the highest enantioselectivity obtained using a chiral catalyst in the hydrogenation of β-(acylamino)acrylates. Moreover, the enantioselectivity of reduction could be improved to 96% ee simply by conducting the reaction at atmospheric pressure. Increasing hydrogen pressure to 100 atm resulted in a decrease in enantiomeric excess to 88%. It should be noted that (*Z*)-**4a** is more reactive than (*E*)-**4a** as indicated by a competitive reaction using a 1:1 mixture of these stereoisomers. This resulted in selective consumption of the *Z* isomer. No appreciable double bond isomerization was seen during the reaction. Hydrogenation of (*E*)-**4b** in methanol with (*R*)-**13** as catalyst under 4 atm of hydrogen proceeded slowly requiring 120 h for total conversion and provided (*S*)-**5b** in 87%

enantiomeric purity. Use of $Ru(OCOCF_3)_2$[(*R*)-binap] as catalyst in the hydrogenation of (*E*)-**4b** under 4 atm of hydrogen provided (*S*)-**5b** in 90% enantiomeric purity after only 18 h.[23] Again the reaction of the *Z* isomer gave the saturated product **5b** in <5% ee. Under similar conditions, (*E*)-**4c** was hydrogenated to (*R*)-**5c** possessing 90% enantiomeric purity. However, the reaction was slow and required a long period for 100% conversion, during which time the β-amido group was lost and a considerable amount of methyl 3-phenylpropionate was produced such that the desired **5c** was obtained in only 25% yield. Loss of the β-amido group may have occurred either by direct hydrogenolytic cleavage of the benzylic amido group or β-elimination and subsequent hydrogenation of the α,β-unsaturated ester. No methyl cinnamate was detected in the reaction mixture. Separate hydrogenation of (*E*)-methyl cinnamate under identical conditions formed methyl 3-propionate in only 20% yield. The (*R*)-BINAP—Ru catalyzed hydrogenation of (*Z*)-**4c** proceeded smoothly but afforded **5c** in only 9% ee. Hydrogenation of (*E*)-**9** with Ru(II) catalyst (*R*)-**13** at 4 atm hydrogen proceeded smoothly to produce (*R*)-*N*-methylacetamido ester **10** in 60% ee without any loss of the β-acetamido group. Similarly hydrogenation of (*Z*)-**9** cleanly produced (*R*)-**10** in 84% ee.



(*R*) -13



(*R*) -14

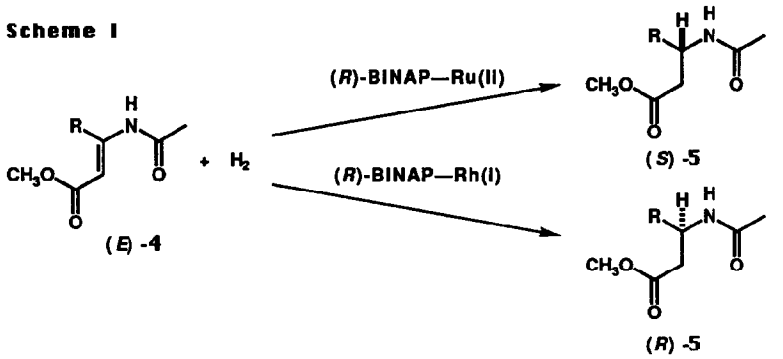
Table I. Asymmetric Hydrogenation of Enamido Esters **4** and **9** Catalyzed by $Ru(OCOCH_3)_2$[(*R*)-binap][a]

				products **5**[b] and **10**		
entry	substrate	H_2, atm	time, h	% conversion	% ee	confign
1	(*E*)-**4a**	1	19	100	96	*S*
2	(*E*)-**4a**	4	20	100	92	*S*
3	(*E*)-**4a**	100	19	100	88	*S*
4	(*Z*)-**4a**	4	20	100	5	*R*
5	(*E*)-**4b**	4	120	100	87	*S*
6[c]	(*E*)-**4b**	4	18	100	90	*S*
7	(*Z*)-**4b**	4	50	60	<5	-
8	(*E*)-**4c**	4	100	100	90	*R*
9	(*Z*)-**4c**	4	16	100	9	*R*
10	(*E*)-**9**	4	20	100	60	*R*
11[d]	(*Z*)-**9**	4	100	97	84	*R*

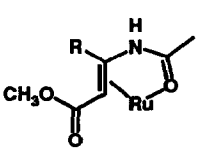
[a] Reactions were carried out in methanol at 0.2 M solution of the substrate at 25 °C in the presence of 0.5 mol % of $Ru(OCOCH_3)_2$(binap). [b] Products from hydrogenation of **4a**, (*E*)-**4b** and (*Z*)-**4c** were obtained quantitatively and converted to **8** and **11** without further purification. Product from (*E*)-**4c** was obtained in 25% yield after chromatography. [c] $Ru(OCOCF_3)_2$(binap) was used as catalyst. [d] Reaction was 0.1 M with respect to substrate.

The catalyst [Rh((*R*)-binap)$(CH_3OH)_2$]ClO_4 [(*R*)-**14**] was next employed in the hydrogenation of enamido ester **4**. In contrast to the ruthenium catalyzed reaction, when this cationic Rh(I) catalyst was used hydrogenation of either enamido ester (*E*)-**4a** or (*Z*)-**4a** in methanol at 4 atm hydrogen produced β-amido ester (*R*)-**5a** possessing similarly modest enantiomeric purity ranging from 45 to 60% ee. Thus Rh(I) catalyst **14** was shown to be insensitive to the olefin geometry of enamido ester **4a** and less enantioselective than the ruthenium catalyst when employed in the hydrogenation of (*E*)-enamido ester (*E*)-**4a**.

Scheme I



Thus we have found that enantioselective hydrogenation of (*E*)-enamido esters in the presence of a chiral BINAP—Ru(II) complex provides a useful method to prepare certain β-amino acids of high enantiomeric purity. Selective synthesis of the *E* substrates through photochemical isomerization and crystallization further improves this method. In addition, this reaction has revealed several characteristic features of BINAP-transition metal catalyzed hydrogenation which are expected and unexpected from previous findings with enamide substrates of type **1**—**3**. In the hydrogenation of enamido ester **4** the BINAP—Ru complexes proved again to be better catalysts than the Rh analogues. The sense of asymmetric induction for the BINAP—Ru complexes was opposite the BINAP—Rh complexes when delivering hydrogen to the olefin to create the amide-bearing stereocenter (Scheme I). The direction of hydrogen delivery is consistent with those observed with enamide substrates **1** and **2**. Most surprising to us is the substituent effect on the reactivity and selectivity in the Ru catalyzed reaction of **4**. In contrast to the highly enantioselective hydrogenations of geometrically constrained substrates **2** and **3** where only *Z* isomers are reactive, hydrogenation of *Z* isomers of enamido esters **4** proceeds with a low degree of enantioselectivity despite the higher reactivity of the *Z* isomers which for (*Z*)-**4a** is 10 times higher than (*E*)-**4a**. Transition metal aided hydrogenation of functionalized olefins is generally considered to proceed by way of a metal chelate complex in which the carbon-carbon double bond and a functional group heteroatom are simultaneously coordinated to the metallic center.[24,25] The substrate (*E*)-**4** possesses amide and ester functional groups but the oxygen in the amide functionality probably acts as the triggering atom causing the Ru promoted reaction by way of complex **15**. The peculiar behavior of (*Z*)-**4** is a result of intramolecular hydrogen-bonded structure **16** which may allow the amide to coordinate the metallic center while preventing coordination of the olefin to form a Ru chelate complex **17**.[19] Hydrogenation of (*Z*)-**4** may thus proceed by way of a 1,4 hydride addition mechanism triggered by the amide. When hydrogen is replaced by methyl as in (*Z*)-**9** hydrogenation can again proceed by complex **17** and high enantioselectivity is obtained.



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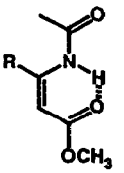

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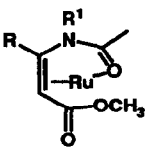

17, R^1 = H, CH_3

Experimental

General. Tetrahydrofuran (THF) was distilled from sodium benzophenone and methanol (MeOH) was distilled from Mg. Solutions were degassed under vacuum after freezing with liquid nitrogen. Final reaction mixture solutions were dried over $MgSO_4$. Column chromatography was on 230—400 mesh silica gel. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ and are reported in ppm (δ units) downfield of internal tetramethylsilane. Mass spectral data was obtained by electron-impact ionization on a JEOL DX-303 spectrometer.

(*Z*)-Methyl 3-Acetamido-2-butenoate [(*Z*)-4a], (*E*)-Methyl 3-Acetamido-2-butenoate [(*E*)-4a], and Methyl 3-Amino-2-(acetyl)-2-butenoate (7a). A solution of methyl 3-amino-2-butenoate (7 g, 0.06 mol, Aldrich), pyridine (8 mL, 0.1 mol), and acetic anhydride (31.2 mL, 0.33 mol) in THF (60 mL) was heated to a reflux (bath temp 90—100 °C), stirred for 15 h, cooled to room temperature, then partitioned between 100 mL of saturated K_2CO_3 and 100 mL ethyl acetate (EtOAc). The organic layer was washed with saturated K_2CO_3 (2 x 50 mL), 1 M KH_2PO_4 (3 x 50 mL), and brine (50 mL), dried and evaporated to an oil which was chromatographed with a gradient of 5—25% EtOAc in hexane as eluant. First to elute was (*Z*)-**4a** (4 g, 42%): mp 39—42 °C; ^1H NMR δ 2.14 (s, 3 H), 2.37 (d, 3 H, J = 1), 3.69 (s, 3 H), 4.89 (d, 1 H, J = 1), 11.06 (br s, 1 H); ^{13}C NMR δ 21.6, 24.9, 50.7, 89.9, 155, 168.6, 169.3; Anal. Calcd for $C_7H_{11}NO_3$: C, 53.4; H, 7.1; N, 8.9. Found: C, 53.4; H, 7.2; N, 8.9. Next to elute was **7a** (980 mg, 11%): mp 96—98 °C; ^1H NMR δ 2.22 (s, 3 H), 2.28 (s, 3 H), 3.75 (s, 3 H). Last to elute was (*E*)-**4a** (2.49 g, 26%): mp 113—114 °C; ^1H NMR δ 2.1 (s, 3 H), 2.34 (s, 3 H), 3.67 (s, 3 H), 6.75 (s, 1 H), 6.9 (br s, 1 H); ^{13}C NMR δ 18.4, 24.9, 50.9, 102.1, 149.3, 168.9, 169.7; Anal. Calcd for $C_7H_{11}NO_3$: C, 53.4; H, 7.1; N, 8.9. Found: C, 53.6; H, 7.2; N, 8.9.

Methyl 3-Acetamidobutanoate (5a). (*E*)- and (*Z*)-Enamido esters **4a** (157 mg, 1.0 mmol) were dissolved in 5 mL of MeOH and the solution was degassed three times, then treated with $Ru(OCOCH_3)_2$[(*R*)-binap] [(*R*)-**13**, 4 mg, 0.005 mmol] and degassed two more times. The solution was transferred under a positive pressure of argon via stainless steel cannula into a pressure vessel that was filled, vented and refilled with a hydrogen atmosphere five times. The solution was stirred for 24 h at room temperature at which time ^1H NMR indicated 100% conversion. Methanol was then evaporated leaving an oil, β-amido ester **5a**: ^1H NMR δ 1.19 (d, 3 H, J = 6.9), 1.93 (s, 3 H), 2.49 (d, 2 H, J = 4.9), 3.66 (s, 3 H), 4.31 (m, 1 H), 6.16 (br m, 1 H); ^{13}C NMR δ 19.8, 23.1, 39.9, 42, 51.4, 169.3, 171.9. Crude β-amido ester **5a** was converted directly to diastereomeric derivatives for enantiomeric purity analysis. Racemic **5a** was prepared under similar conditions with 5 wt % Pd on carbon (80 mg) as catalyst. Removal of the catalyst by filtration through Celite and

evaporation of solvent gave **5a** (154 mg, 98%) as a clear oil which crystallized on standing: mp 47—48 °C; Anal. Calcd for $C_7H_{13}NO_3$: C, 52.8; H, 8.2; N, 8.8. Found: C, 52.7; H, 8.2; N, 8.8.

Reduction of β-Acetamido Esters 5 to Ethylamino Alcohols 11. Crude β-amido ester (1 mmol) in 10 mL of THF was cooled to 0 °C, treated with 200 mg of $LiAlH_4$ (5 mmol), stirred for 30 min, then heated to reflux, and stirred for 2 h. The mixture was cooled to 0 °C, treated with 5 mL of EtOAc, stirred 2 min, treated with 1 mL of saturated $KHSO_4$, dried with $MgSO_4$, and filtered through a plug of $MgSO_4$. The plug was washed with 3 x 15 mL of EtOAc, and the combined solvent was evaporated to the amino alcohol, which was directly coupled to the thioisocyanate and analyzed on HPLC.

3-Ethylamino-1-butanol (11a) (68%): oil; ^1H NMR δ 1.06 (t, 3 H, J = 7), 1.11 (d, 3 H, J = 6.6), 1.5 (m, 1 H), 1.65 (m, 1 H), 2.02 (br s, 1 H), 2.58 (m, 1 H), 2.75 (m, 1 H), 2.9 (m, 1 H), 3.79 (m, 2 H); ^{13}C NMR δ 62.2, 54.1, 41, 36.8, 20.3, 15.4; mass spectrum, *m/z* 117 (M^+, 24), 102 (93), 84 (100).

3-Ethylamino-5-methyl-1-hexanol (11b) (94%): oil; ^1H NMR δ 0.83 (d, 3 H, J = 6.4), 0.86 (d, 3 H, J = 5.9), 1.02 (t, 3 H, J = 7.2), 1.2 (m, 1 H), 1.39 (m, 2 H), 1.55 (m, 1 H), 1.7 (m, 1 H), 2.6 (m, 2 H), 2.77 (m, 1 H), 3.78 (m, 2 H); ^{13}C NMR δ 62.5, 56.7, 43.6, 40.7, 33.4, 25, 23.3, 22.3, 15.4; mass spectrum, *m/z* 159 (M^+, 4), 114 (67), 102 (100).

3-Ethylamino-3-phenyl-1-propanol (11c) (85%): mp 91—93 °C; ^1H NMR δ 1 (t, 3 H, J = 7), 1.9 (m, 2 H), 2.45 (m, 2 H), 3.75 (m, 3 H), 7.3 (m, 5 H); ^{13}C NMR δ 15.3, 38.4, 41.5, 62.9, 64.1, 126.4, 127.3, 128.7, 143.3; Anal. Calcd for $C_{11}H_{17}NO$: C, 73.7; H, 9.6; N, 7.8. Found: C, 73.6; H, 9.5; N, 7.7.

Preparation of Thioureas.[21] Ethylamino alcohol (1 mg) in 100 μL CH_3CN was treated with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (GITC, 3 mg), stirred 10 min and diluted with 1 mL of CH_3CN. Thioureas of 3-ethylamino-1-butanol (**11a**), 3-ethylamino-5-methyl-1-hexanol (**11b**), 3-ethylamino-3-phenyl-1-propanol (**11c**), and 3-methylamino-3-phenyl-1-propanol (**12**) were analyzed with reversed phase HPLC using an ODS column and mobile phases of 2:3, 1:1, 1:1, and 45:55 CH_3CN:H_2O containing 1.4 g of $NH_4H_2PO_4$ / 600 mL H_2O as eluant. HPLC analysis of thiourea produced from racemic **5** and **10** showed two peaks of equal intensity. Thiourea isomers produced from (*S*)-**5a**, (*S*)-**5b**, (*R*)-**5c**, and (*R*)-**10** were eluted last.

(*E*)-Methyl 3-Acetamido-5-methyl-2-hexenoate [(*E*)-4b], (*Z*)-Methyl 3-Acetamido-5-methyl-2-hexenoate [(*Z*)-4b] and Methyl 3-Amino-2-(acetyl)-5-methyl-2-hexenoate (7b). A 0 °C solution of Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione, 3 g, 21 mmol) and pyridine (3.4 mL, 42 mmol) in 40 mL of CH_2Cl_2 was treated dropwise with isovaleryl chloride (2.8 mL, 23 mmol), stirred for 2 h, warmed to room temperature and stirred for an additional 2 h. The solution was washed with 1 N HCl (40 mL), water (40 mL) and brine (40 mL), dried, and evaporated to an oil which was redissolved in 40 mL of MeOH and heated at a reflux for 18 h. Solvent was evaporated and the residue was chromatographed with 12% EtOAc in hexane as eluant. Evaporation of the collected fractions gave methyl 3-oxo-5-methylhexanoate: 2 g, 61%; ^1H NMR δ 0.92 (d, 6 H, J = 6.4), 2.12 (m, 1 H), 2.4 (d, 2 H, J = 7), 3.4 (s, 2 H), 3.72 (s, 3 H).

Methyl 3-oxo-5-methylhexanoate[20] (1.9 g, 12 mmol) was dissolved in 15 mL of MeOH, treated with 4.6 g of NH_4OAc, and stirred for 3 days. Evaporation of the volatiles gave a solid which was washed with $CHCl_3$ (25 mL), filtered, and then washed again with 2 x 25 mL $CHCl_3$. The combined $CHCl_3$ filtrate was

washed with water (25 mL) and brine (25 mL), dried and evaporated to methyl 3-amino-5-methyl-2-hexenoate (**6b**) as a clear oil: ^{1}H NMR δ 0.94 (d, 6 H, J = 6.2), 1.86 (m, 1 H), 1.97 (d, 2 H, J = 6.6), 3.64 (s, 3 H), 4.5 (s, 1 H). This enamino ester was dissolved in 12 mL of THF, treated with 2 mL of pyridine and 6 mL of acetic anhydride, and heated at a reflux for 24 h. The solution was evaporated to one quarter of its original volume, diluted with 10 mL EtOAc, washed with water (10 mL), 1 N HCl (2 x 10 mL), saturated $NaHCO_3$ (2 x 10 mL) and brine (10 mL), dried, and evaporated to a residue which was chromatographed with a gradient of 12—60% EtOAc in hexane as eluant. First to elute was (*Z*)-methyl 3-acetamido-5-methyl-2-hexenoate [(*Z*)-**4b**], 1.0 g, 42%; an oil; ^{1}H NMR δ 0.88 (d, 6 H, J = 6.5), 1.86 (m, 1 H), 2.09 (s, 3 H), 2.52 (dd, 2 H, J = 2, 6.6), 3.65 (s, 3 H), 4.85 (s, 1 H) 10.96 (br s, 1 H); ^{13}C NMR δ 169.5, 168.4, 157.9, 96.6, 51, 43.1, 26.9, 25.4, 22.1. Next to elute was methyl 3-amino-2-(acetyl)-5-methyl-2-hexenoate (**7b**), 160 mg, 7%; ^{1}H NMR δ 0.9 (d, 6 H, J = 6.4), 1.84 (m, 1 H), 2.2 (s, 3 H), 2.33 (d, 2 H, J = 7.4), 3.7 (s, 3 H), 5.9 (br s, 1 H). Last to elute was (*E*)-methyl 3-acetamido-5-methyl-2-hexenoate [(*E*)-**4b**], 380 mg, 16%; mp 128—130 °C; ^{1}H NMR δ 0.98 (d, 6 H, J = 6.6), 1.89 (m, 1 H), 2.11 (s, 3 H), 2.66 (d, 2 H, J = 7.6), 3.67 (s, 3 H), 6.57 (br s, 1 H), 6.9 (s, 1 H); ^{13}C NMR δ 169.8, 168.7, 152.4, 102.8, 50.8, 39.6, 28, 25, 22; Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.3; H, 8.6; N, 7.0. Found: C, 60.4; H, 8.6; N, 7.0.

Methyl 3-Acetamido-5-methylhexanoate (5b). Acetamido esters (*E*)-**4b** and (*Z*)-**4b** were hydrogenated using similar conditions as those described to prepare amidobutanoate **5a**. Methyl 3-acetamido-5-methylhexanoate (**5b**) was obtained as an oil: ^{1}H NMR δ 0.86 (d, 6 H, J = 6.4), 1.24 (m, 1 H), 1.5 (m, 2 H), 1.93 (s, 3 H), 2.43 (dd, 1 H, J = 5, 16), 2.53 (dd, 1 H, J = 5, 15.8), 3.64 (s, 3 H), 4.27 (m, 1 H), 6.1 (br d, 1 H, J = 9); ^{13}C NMR δ 172.4, 169.5, 51.6, 44.1, 43.1, 38.7, 25, 23.4, 22.9, 22.1; Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.7; H, 9.5; N, 7.0. Found: C, 60; H, 9.9; N, 6.8. (*S*)-(−)-Methyl 3-acetamido-5-methylhexanoate [(*S*)-**5b**] of 90% ee as determined by HPLC analysis gave the following optical rotation: $[\alpha]^{25}_D$ −42 (*c*, 1.06 in $CHCl_3$).

(*Z*)-Methyl 3-Acetamido-3-phenyl-2-propenoate [(*Z*)-4c], and (*E*)-Methyl 3-Acetamido-3-phenyl-2-propenoate [(*E*)-4c]. Ethyl benzoylacetate (1 mL, 5.7 mmol) was added to a solution of acetyl chloride (1 mL) in 10 mL of MeOH and stirred for 16 h. The solution was evaporated in a rotary evaporator to a residue that was let sit under high vacuum overnight. The residue was dissolved in 10 mL of MeOH, treated with 2.6 g of NH_4OAc (34 mmol), and stirred for 5 days at room temperature. The MeOH was evaporated and the residue was triturated with $CHCl_3$ (5 x 10 mL). Evaporation of the $CHCl_3$ left a residue that was dissolved in 5 mL of THF and treated with pyridine (0.5 mL) and acetic anhydride (2.5 mL). The solution was heated to a reflux, stirred for 24 h, cooled to room temperature, then partitioned between 10 mL of saturated K_2CO_3 and 20 mL EtOAc. The organic layer was washed with saturated K_2CO_3 (2 x 5 mL), 1 M KH_2PO_4 (3 x 5 mL), and brine (10 mL), dried, and evaporated to an oil which was chromatographed with a gradient of 0—10% EtOAc in hexane as eluant. Evaporation of the collected fractions provided a 1.4:1 mixture of enamido esters **4c** (840 mg, 67%). First to elute was (*Z*)-**4c**; mp 71—73 °C; ^{1}H NMR δ 2.18 (s, 3 H), 3.78 (s, 3 H), 5.27 (s, 1 H), 7.38 (br s, 5 H), 10.6 (br s, 1 H); ^{13}C NMR δ 24.7, 51.4, 100.6, 127, 128, 129.6, 135.9, 154.7, 168.4, 169. Next to elute was (*E*)-**4c**; mp 95—96 °C; ^{1}H NMR δ 2.38 (s, 3 H), 3.79 (s, 3 H), 6.61 (s, 1 H), 7.42 (m, 6 H); ^{13}C NMR δ 26, 52, 116.6, 126.1, 129.3, 131.1, 135, 150.3, 164.5, 172.2; Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.6; H, 6.0; N, 6.4. Found: C, 65.5; H, 6.0; N, 6.3.

Methyl 3-Acetamido-3-phenylpropanoate (5c). Acetamido esters (*E*)-**4c** and (*Z*)-**4c** were hydrogenated using similar conditions as those described to prepare methyl 3-acetamidobutanoate (**5a**). Methyl 3-acetamido-3-phenylpropanoate (**5c**): ^{1}H NMR δ 2.01 (s, 3 H), 2.79 (dd, 1 H, *J* = 15.8, 6), 2.93 (dd, 1 H, *J* = 15.8, 6), 3.61 (s, 3 H) 5.42 (dt, 1 H, *J* = 6, 7) 6.64 (br s, 1 H), 7.33 (m, 5 H); ^{13}C NMR δ 23.5, 39.8, 49.5, 51.9, 126.3, 127.7, 128.8, 140.5, 169.4, 171.8; racemic **5c**, mp 76—78 °C; Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.1; H, 6.8; N, 6.3. Found: C, 65.1; H, 6.8; N, 6.2.

Synthesis of β-Amino Acids 8. Acetamido ester **5** [from hydrogenation of (*E*)-**4** (2 mmol) with $Ru(OCOCH_3)_2$[(*R*)-binap] [(*R*)-**13**] as catalyst] was dissolved in 2 mL of THF and 10 mL of 6 N HCl and heated at a reflux for 19 h. The reaction was cooled to room temperature and evaporated to a residue that was purified on 20 g of Dowex 1-X1 resin (hydroxide form) with a gradient of 0—0.5 M acetic acid as eluant. Evaporation of the ninhydrin positive fractions gave desired β-amino acids **8**.

(*S*)-(+)-3-**Aminobutanoic Acid (8a)**: 74% from (*E*)-**5a**, recrystallized from MeOH; mp 212 °C; $[\alpha]^{26}_D$ +34.3° (*c*, 1.12 in water); lit.[10a] mp 212 °C; $[\alpha]^{19}_D$ +37.07 (*c*, 6.0 in water).

(*S*)-(+)-**3-Amino-5-methylhexanoic Acid (8b)**: 85% from (*E*)-**5b**, precipitated from ethanol with ether; mp 215—216 °C; $[\alpha]_D$ +26.7 (*c*, 0.6 in water); lit.[26] mp 215—216 °C; $[\alpha]_D$ +25.1 (*c*, 0.815 in water); lit.[11] mp 215—216 °C; $[\alpha]_D$ +28.0 (*c*, 3 in water).

(*E*)-**Methyl 3-*N*-Methylacetamido-3-phenyl-2-propenoate [(*E*)-9].** Methyl 3-acetamido-3-phenyl-2-propenoate (**4c**, 750 mg, 3.4 mmol) in 30 mL of THF was treated with NaH (210 mg, 50 wt %, 4.2 mmol) and stirred for 20 min at room temperature. The solution was treated with methyl iodide (425 μL, 6.8 mmol), heated to 60 °C, and stirred for 1 h. The mixture was cooled to 0 °C, partitioned between 20 mL of EtOAc and 20 mL of 1 M NaH_2PO_4, and the aqueous layer was extracted with 2 x 10 mL of EtOAc. The combined organic layers were washed with brine, dried, and evaporated to a residue that was chromatographed with a gradient of 25—50% EtOAc in hexane as eluant. Evaporation of the collected fractions gave a white crystalline solid, (*E*)-**9**: mp 61—63 °C; ^{1}H NMR δ 1.96 (s, 3 H), 3.05 (s, 3 H), 3.78 (s, 3 H), 6.35 (s, 1 H), 7.45 (m, 5 H); ^{13}C NMR δ 170.3, 164.6, 153.8, 134.9, 131.1, 129.2, 126.8, 114.4, 51.8, 34.9, 21.3; Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.9; H, 6.5; N, 6.0. Found: C, 66.8; H, 6.5; N, 5.9.

(*Z*)-**Methyl 3-*N*-Methylacetamido-3-phenyl-2-propenoate [(*Z*)-9]** was obtained after chromatography of a 3:2 mixture of *E*:*Z* isomers obtained from exposure of pure (*E*)-**9** in $CHCl_3$ to light from a Hg lamp for 100 h. (*Z*)-**9**: mp 96—98 °C; ^{1}H NMR δ 2.13 (s, 3 H), 2.98 (s, 3 H), 3.64 (s, 3 H), 5.87 (s, 1 H), 7.4 (m, 5 H); ^{13}C NMR δ 170.9, 166, 155.4, 134.1, 130.5, 129.1, 128.5, 115.5, 51.7, 35.7, 22.8.

Methyl 3-*N*-Methylacetamido-3-phenylpropanoate (10). *N*-Methylacetamido esters (*E*)-**9** and (*Z*)-**9** were hydrogenated using similar conditions as those described to prepare (**5a**). Methyl 3-*N*-methylacetamido-3-phenylpropanoate (**10**): racemic mp 89—90 °C; NMR spectroscopy indicated **10** to exist as a 1:1 mixture of amide rotamers; ^{1}H NMR δ 2.03 (s, 3 H), 2.26 (s, 3 H), 2.6 (s, 3 H), 2.64 (s, 3 H), 2.86 (m, 4 H), 3.59 (s, 3 H), 3.65 (s, 3 H), 5.4 (dd, 1 H, *J* = 5.4, 9.4), 6.26 (dd, 1 H, *J* = 6.9, 8.4), 7.25 (m, 10 H).^{13}C NMR δ 171.2, 171.1, 138.5, 137.9, 129, 128.6, 128.1, 127.7, 127.2, 126.3, 57.1, 52.3, 52.2, 52, 36.5, 35.2, 30.8, 27.6, 22.2, 21.6. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.4; H, 7.3; N, 5.9. Found: C, 66.2;

H, 7.3; N, 5.9. (*R*)-(+)-Methyl 3-*N*-methylacetamido-3-phenylpropanoate (**10**) of 60% ee as determined by HPLC analysis gave the following optical rotation: $[\alpha]^{25}_{D}$ +53 (*c*, 0.46 in $CHCl_3$).

3-Methylamino-3-phenyl-1-propanol (12). A –78 °C solution of crude 3-*N*-methylacetamido ester **10** (180 mg, 0.77 mmol) in THF (8 mL) was treated with $LiAlH_4$ (160 mg, 4 mmol), stirred for 2.5 h, and treated with 8 mL of EtOAc. The solution was quenched with saturated $KHSO_4$ (1 mL), warmed to room temperature, dried with $MgSO_4$, and filtered through a pad of $MgSO_4$ which was washed with 2 x 10 mL of EtOAc. Evaporation of the volatiles gave an oil containing >95% pure 3-*N*-methylacetamido-3-phenyl-1-propanol: ^1H NMR δ 2.0 (m, 1 H), 2.19 (s, 3 H), 2.57 (s, 3 H), 2.68 (m, 1 H), 3.46 (m, 1 H), 3.67 (m, 1 H), 6.01 (dd, 1 H, J = 12.4, 3.5), 7.3 (m, 5 H); ^{13}C NMR δ 172.7, 138.9, 128.6, 128, 127.7, 58.4, 51.8, 31.4, 30.7, 22.

Crude 3-*N*-methylacetamido-3-phenyl-1-propanol was dissolved in 4 mL of MeOH, treated with 4 mL of 6 N HCl, and heated at a reflux for 19 h. The solution was cooled to room temperature, diluted with 4 mL of water, and extracted with 2 x 7 mL of Et_2O. The aqueous solution's pH was adjusted to ca. 12 by addition of solid K_2CO_3, and the basic solution was extracted with 5 x 10 mL of EtOAc. The combined organic extractions were dried and evaporated to an oil which was directly coupled to the thioisocyanate and analyzed on HPLC. 3-Methylamino-3-phenyl-1-propanol (**12**), crystallized on treatment with hexane, 110 mg, 87% from **10**: mp 56—57 °C; NMR δ 1.9 (m, 1 H), 2 (m, 1 H), 2.29 (s, 3 H), 3.78 (m, 3 H), 3.99 (br s, 2 H), 7.3 (m, 5 H); ^{13}C NMR δ 141.9, 128.7, 127.6, 126.8, 65.3, 61.9, 38.2, 33.6; Anal. Calcd for $C_{10}H_{15}NO$: C, 72.7; H, 9.2; N, 8.5. Found: C, 72.7; H, 9.2; N, 8.2. Methylamino alcohol **12**

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References and Notes

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18. To distinguish between the allylic and amido methyl group singlets in the proton NMR of **4a** the proton spectrum was first correlated to the carbon spectrum and the carbon assignments were determined by INADEQUATE spectroscopy. Assignments of the configuration of (*Z*)- and (*E*)-enamido esters **4c** and **9** are based on analogy with **4a** and **4b** and the assumption that the vinyl proton is shifted further down field for the *E* isomers.
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21. (a) Gal, J. *J. Chromatography* **1984**, *307*, 220. (b) Nimura, N.; Ogura, H.; Kinoshita, T. *J. Chromatography* **1980**, *202*, 375. (c) Kinoshita, T.; Kasahara, Y.; Nimura, N. *J. Chromatography* **1981**, *210*, 77.
22. 3-Acetamidobutanoic acid, [^{1}H NMR δ 1.22 (d, 3 H, J = 6.4), 1.96 (s, 3 H), 2.51 (d, 2 H, J = 5.4), 4.35 (m, 1 H), 6.7 (d, 1 H, J = 8.4); ^{13}C NMR δ 19.9, 23.1, 40, 42.4, 170.8, 175.] prepared by hydrolysis of **5a** with 2:3 THF : 1 M LiOH for 3 h at room temperature, was dissolved in CH_2Cl_2 (0.1 M), cooled to 0 °C, treated with 220 mol % of Et_3N and 120 mol % of $(COCl)_2$, stirred for 30 min, then treated with 150 mol % of (*R*)-(+)-1-(1-naphthyl)ethylamine and stirred for 16 h at room temperature. The solution was washed with water, saturated $NaHCO_3$, 1 M KH_2PO_4 and brine, dried, and evaporated to a residue which was directly analyzed with ^{1}H NMR. Analysis of amide prepared with racemic **5a** showed two doublets of equal intensity at δ 1.22 and 1.13. Amide prepared from (*R*)-(+)-amine and (*S*)-β-amido acid **5a** gave the following NMR spectra: ^{1}H NMR δ 1.22 (d, 3 H, J = 6.4), 1.65 (d, 3 H, J =

7), 1.7 (s, 3 H), 2.23 (dd, 1 H, J = 5.3, 14.8), 2.41 (dd, 1 H, J = 5, 14.4), 4.2 (m, 1 H), 5.9 (m, 1 H), 6.32 (br d, 1 H, J = 7.9), 6.52 (br d, 1 H, J = 7.9), 7.5 (m, 4 H), 7.7 (m, 2 H), 8.05 (m, 1 H); ^{13}C NMR δ 170, 169.7, 138.2, 134, 131, 129, 128.4, 126.6, 125.9, 125.4, 123.3, 122.6, 44.6, 42.8, 41.6, 23.3, 20.8, 20.1.

23. $Ru(OCOCF_3)_2$[(*R*)-binap] was prepared by treating a degassed 0.02 M solution of $Ru(OCOCH_3)_2$[(*R*)-binap] in CH_2Cl_2 with 200 mol % of CF_3CO_2H, degassing, stirring for 16 h at room temperature, and evaporation under high vacuum to a powder. Attempts to hydrogenate (*E*)-**4b** with $Ru(OCOCF_3)_2$[(*R*)-binap] as catalyst at 1 atm H_2 proceeded with less than 5% conversion after 100 h.
24. The mechanism of Rh catalyzed hydrogenation of enamides is presented in: (a) Halpern, J. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985, Vol. 5, Chapter 2; (b) Brown, J. M.; Chaloner, P. A. In *Homogeneous Catalysis with Metal Phosphine Complexes*; Pignolet, L. H., Ed.; Plenum: New York, 1983, Chapter 4. The mechanism of Ru catalyzed hydrogenation of olefins is described in: James, B. R. *Homogeneous Hydrogenation*; John Wiley: New York, 1973, pp 72—103. The mechanism of Ru catalyzed hydrogenation of α,β-unsaturated carboxylic acids is presented in: (a) Ohta, T.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1990**, *49*, 7189; (b) Ashby, M. T.; Halpern, J. *J. Am. Chem. Soc.* **1991**, *113*, 589.
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