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An enantioselective synthesis of β²-amino acid derivatives

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Abstract—Enantioselective hydrogenation of a series of (*E*)-α-substituted β-amidoacrylates using Rh(I)-catalysts with chiral phosphine ligands (BPE, DuPHOS) gives β²-amino acid derivatives with enantioselectivities of up to 67%. A β²,³-amino acid derivative was also synthesised with similar enantioselectivity (⩽65%) from the corresponding prochiral enamide.

1. Introduction

β-Peptides have recently emerged as important building blocks for the construction of new peptidomimetics.[1–5] Their ability to fold into distinct secondary structures akin to α-peptides, including helices,[1,3,6–12] turns,[13,14] sheets[15–18] and tubular structures,[19] and their remarkable stability towards peptidases,[20–24] make them powerful tools for medicinal chemistry and future therapeutic agents. Indeed to date, a cyclic β-tetrapeptide with biological activity similar to that of the α-tetradecapeptide somatostatin, an important neurotransmitter and hormone secretion inhibitor, has been prepared.[25–27] Other applications as protease inhibitors,[28] precursors for antibiotics[29] and as building blocks in cryptophycins[30] have also been established.

The β-amino acids necessary for the synthesis of β-peptides have the potential for two stereogenic centres at C2 (β²-) and C3 (β³-) in the amino acid backbone. A facile synthesis of chiral β³-amino acids exists using the Arndt–Eistert homologation of α-amino acids.[1,31–36] In contrast, routes to chiral β²-amino acids have traditionally required the use of chiral auxiliaries[37] and usually involve chromatographic separation of diastereomers. Seebach et al. reported the preparation of β²-amino acids using the modified Evans oxazolidinone, DIOZ, in which high de values were obtained in the diastereoselective step, in some cases >97%, removing the need for a chromatographic separation.[38] More recently, catalytic routes have been developed to provide enantioselective syntheses of β²-amino acids and include rhodium(I)-catalysed addition of amines to aryldiazoacetates,[39] (salen)Al(III)-catalysed cyanide conjugate addition to α,β-unsaturated imides,[40] palladium-catalysed allylic substitution of allylic acetates,[41] and conjugate addition of dialkylzinc reagents to nitroalkenes.[42]

Herein we report an enantioselective route to β²-amino acid derivatives using Rh(I)-catalysed asymmetric hydrogenation of some α-substituted β-amidoacrylates as the key step. This route to β²-amino acids does not seem to have been explored even though such chemistry has already been reported by us[43,44] and others[45–60] to prepare β³-amino acid derivatives. We also report the synthesis and subsequent hydrogenation of an α,β-disubstituted β-enamide (a β²,³-enamide) to yield a β²,³-amino acid derivative with moderate enantioselectivity.

2. Results and discussion

2.1. Preparation of substrates

An isomeric mixture of the starting enamides **1** was readily prepared from commercially available carboxylic acid esters **2** by deprotonation, reaction with ethyl formate and condensation of the resulting formyl esters **3** with acetamide (Scheme 1). Intramolecular hydrogen-bonding between the β-amide hydrogen and ester carbonyl group in the (*Z*)-isomer was evident in the ^{1}H NMR spectra of the enamides **1** where a significant

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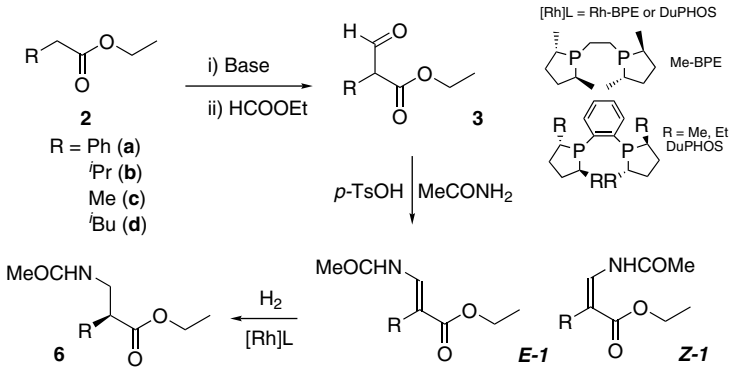
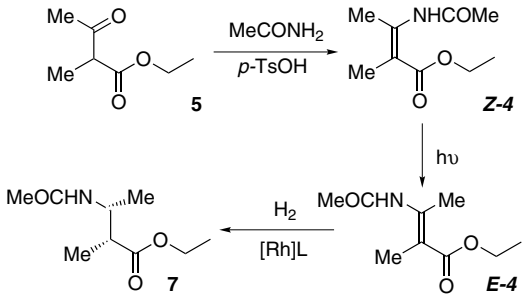


Scheme 1.



Scheme 2.

downfield shift of the β-amide proton (δ 10–11) was observed. The (*E*)- and (*Z*)-isomers were readily separated by conventional column chromatography. Conveniently, the (*E*)-enamide could also be isolated in quantitative yield by the photochemical isomerisation of the (*Z*)-isomer.

Similarly, $\beta^{2,3}$-enamides **4** were prepared by reaction of the acetoacetate derived β-keto ester **5** with acetamide as described previously (Scheme 2). In this case, however, the $\beta^{2,3}$-enamide was isolated solely as the (*Z*)-isomer ***Z*-4**. Photochemical isomerisation of this isomer at room temperature afforded the pure (*E*)-enamide ***E*-4** in quantitative yield.

2.2. Hydrogenation of α-substituted β-amidoacrylates 1

Encouraging results (ee's up to 67%) were obtained for the hydrogenations of (*E*)-enamides ***E*-1** bearing bulky Ph or ^{i}Pr substituents at C2 using (*R*,*R*)-Me–BPE–Rh(I) in methanol and a hydrogen pressure of 60 psi at ambient temperature (Table 1, entries 1 and 2). Less bulky substituents, Me (entry 3) and ^{i}Bu (entry 4), gave lower ee values.

Attempts to improve enantioselectivity involved the modification of the amide group, the chiral ligand and the solvent. Reaction of the benzamide analogue of ***E*-1c** gave complete conversion under identical experimental conditions with a very similar ee (17%) to that recorded for the acetamide in Table 1 (entry 3). Use of the more bulky chiral ligands Me–DuPHOS and Et–DuPHOS had little effect on the ee values obtained for all of the substrates giving slightly lower values for ***E*-1a–c** (Table 2, entries 5–9) but slightly higher values for the isobutyl derivative ***E*-1d** (Table 2, entries 10 and 11).

Table 1. Hydrogenation of (*E*)-enamides **1** using (*R*,*R*)-Me–BPE–Rh(I)[a]

Entry	R	Product	% Ee
1	Ph	**6a**	67
2	^{i}Pr	**6b**	67
3	Me	**6c**	22
4	^{i}Bu	**6d**	<5

[a] Reactions in methanol with H_2 (60 psi) at ambient temperature for 72 h.

Reactions in benzene were sluggish and required a higher hydrogen pressure and an increase in temperature to 50 °C (Table 3) to affect complete conversion. Under Rh(I)–Me–BPE catalysis, only ***E*-1c** reduced with a slightly improved enantioselectivity of 33% (Table 3, entry 17) in this solvent; other substrates (entries 12 and 14) were reduced with significantly lower enantioselectivity. Similarly, the use of Rh(I)–DuPHOS catalysts in benzene did not exhibit marked enhancement of selectivity and in some cases resulted in lower % ee (i.e., entries 16 and 18).

The absolute configuration of the C2-stereogenic centre in **6** was ascertained by chemical correlation with α-substituted β-amino acids of known configuration. Hydrolysis of methyl and phenyl substituted β^2-amino acid derivatives, **6a** and **6c**, respectively, obtained from (*R*,*R*)-Me–BPE–Rh(I)-catalysed reactions yielded the

Table 2. Hydrogenation of (*E*)-enamides **1** using Me–DuPHOS–Rh(I) and Et–DuPHOS–Rh(I)[a]

Entry	R	Ligand	Product	% Ee
5	Ph	(*S*,*S*)-Me–DuPHOS	**6a**	47
6	Ph	(*S*,*S*)-Et–DuPHOS	**6a**	26
7	^{i}Pr	(*R*,*R*)-Et–DuPHOS	**6b**	58
8	Me	(*S*,*S*)-Me–DuPHOS	**6c**	18
9	Me	(*S*,*S*)-Et–DuPHOS	**6c**	8
10	^{i}Bu	(*S*,*S*)-Me–DuPHOS	**6d**	10
11	^{i}Bu	(*S*,*S*)-Et–DuPHOS	**6d**	14

[a] Reactions in methanol with H_2 (60 psi) at ambient temperature for 72 h.

Table 3. Hydrogenation of (*E*)-enamides **1** using Et–DuPHOS–Rh(I), Me–DuPHOS–Rh(I) and Me–BPE–Rh(I)[a]

Entry	R	Ligand	Product	% Ee
12	Ph	(*R*,*R*)-Me–BPE	**6a**	5
13	Ph	(*S*,*S*)-Et–DuPHOS	**6a**	33
14	^{i}Pr	(*R*,*R*)-Me–BPE	**6b**	32
15	^{i}Pr	(*R*,*R*)-Me–DuPHOS	**6b**	23
16	^{i}Pr	(*R*,*R*)-Et–DuPHOS	**6b**	31
17	Me	(*R*,*R*)-Me–BPE	**6c**	33
18	Me	(*S*,*S*)-Me–DuPHOS	**6c**	12
19	Me	(*S*,*S*)-Et–DuPHOS	**6c**	16

[a] Reactions in benzene with H_2 (90 psi) at 50 °C for 72 h.

known (*R*)-β^2-amino acids. It is therefore highly likely that analogous reactions conducted with isopropyl and isobutyl substituted enamides, **1b** and **1d**, respectively, also afford (*R*)-configured products.

The α-substituted (*Z*)-enamides were found to be less susceptible to hydrogenation than the corresponding (*E*)-isomers. Only the (*Z*)-isomer of **1a** and **1c** underwent hydrogenation at elevated temperature and pressure. In both cases, only poor enantioselection (<15%) was achieved. The lower reactivity of the (*Z*)-isomers may be due to formation of an intramolecular hydrogen bond between the amido NH and ester carbonyl group, which prevents bidentate chelation of the substrate to the catalyst metal centre.

2.3. Hydrogenation of an α,β-disubstituted β-amidoacrylate *E*-4

The synthesis and subsequent hydrogenation of the (*Z*)-α,β-disubstituted β-enamide ***Z*-4** has been reported by Zhang and co-workers.[61] Zhang used an in situ generated Ru(II)–biaryl chiral catalyst with high hydrogen pressure (735 psi) to produce the (2*S*,3*R*)-*threo* isomer in 72% ee. We envisaged that the corresponding (*E*)-enamide would require milder hydrogenation conditions and lead to products with high enantioselectivity. Hydrogenation of the (*E*)-enamide using (*R*,*R*)-Me–BPE–Rh(I) in methanol and a hydrogen pressure of 60 psi at ambient temperature yielded the (2*R*,3*R*)-*erythro* $\beta^{2,3}$-amino acid derivative **7** in 48% ee (Table 4, entry 20). No trace of *threo* stereoisomers was detected by chiral GC under conditions, which led to base line separation of all four stereoisomers. All four stereoisomers of **7** were obtained from a Pd/C hydrogenation of ***E*-4**: A 1.8:1 ratio of *erythro* to *threo* stereoisomers was detected via this route suggesting that some in situ $E \rightleftharpoons Z$ equilibration occurs under these conditions. Rh(I)–BPE-catalysed hydrogenation of ***E*-4** over 14 h also went to completion and gave an identical ee (49%, entry 21). A similar reaction conducted at one atmosphere of hydrogen pressure was complete after 96 h and resulted in a product with 35% ee (entry 22). Use of benzene as a solvent required 90 psi of hydrogen pressure for quantitative conversion to **7** but resulted in increased enantioselectivity (65% ee, entry 23). Attempts to further improve enantioselectivity involved the use of the more sterically demanding chiral ligands Me–DuPHOS and Et–DuPHOS. Unfortunately, hydrogenation reactions employing these Rh(I)-catalysts in methanol led to products with only poor enantiomeric excess (<15% ee, entries 24–26).

2.4. Mechanistic comments

The poor enantioselectivity obtained from Rh(I)–BPE/DuPHOS-catalysed hydrogenation of the α-substituted β-amidoacrylates was surprising in light of the excellent selectivity obtained from asymmetric hydrogenation of β-substituted β-amidoacrylates under the same reaction conditions. As for the β-substituted β-amidoacrylates, the sense of enantioselection observed in the reduction of the α-substituted β-amidoacrylates was found to be the opposite to that observed for α-amidoacrylates.[62] Recent computational data[63] and detailed mechanistic studies[64] on Rh-catalysed hydrogenation of β-amidoacrylates support an alternative mechanistic pathway to that of α-amidoacrylate reduction, which involves the preferential binding of the α-carbon to rhodium via initial hydrogen transfer to the β-position. The lack of a β-substituent in enamides **1a**–**d** may contribute to the reduced stereoselectivity we observed, as it may be playing a key stereoregulating role via steric interaction with ligand alkyl groups. It is noteworthy that Rh–BPE-catalysed reduction of *E*-enamides **1a** and **4** (the β-methyl analogue of **1**) under analogous conditions gives 33% and 65% ee (in benzene) and 22% and 48% ee (in methanol), respectively. Here the inclusion of a small methyl substituent at the β-position approximately doubles enantioselectivity. The mechanistic origin of the 'reversed sense of chirality' and lower than expected enantioselectivity may be provided through future low temperature NMR studies of intermediate monohydride species.

3. Conclusion

In conclusion, we have developed the first enantioselective synthesis of β^2-amino acid derivatives using

Table 4. Hydrogenation of (*E*)-enamide **4** using Rh(I)-catalysts at ambient temperature

Entry	Ligand	Solvent	H_2 pressure (psi)	Reaction time (h)	% Ee
20	(*R*,*R*)-Me–BPE	Methanol	60	72	48
21	(*R*,*R*)-Me–BPE	Methanol	60	14	49
22	(*R*,*R*)-Me–BPE	Methanol	15	96	35
23	(*R*,*R*)-Me–BPE	Benzene	90	72	65
24	(*S*,*S*)-Me–DuPHOS	Methanol	60	72	14
25	(*S*,*S*)-Me–DuPHOS	Methanol	15	72	5
26	(*S*,*S*)-Et–DuPHOS	Methanol	60	72	8

catalytic asymmetric hydrogenation as the key step. The novel α-substituted β-enamides were readily prepared and hydrogenated under mild conditions to afford products with moderate enantioselectivity up to 67% ee. The synthesis and hydrogenation of an α,β-disubstituted β-enamide ***E*-4** was also investigated and this substrate was found to reduce with improved enantioselectivity compared to analogous reactions performed with the α-substituted β-enamide ***E*-1c**. The ease of formation of the hydrogenation substrates from inexpensive and readily available starting materials makes this route to β^2-amino acids particularly attractive. Further investigation of other chiral hydrogenation catalysts is underway and should result in improved hydrogenation enantioselectivity.

4. Experimental

4.1. General

Melting points were determined using a Reichert hot-stage melting point apparatus and are uncorrected. Microanalyses were performed either by Chemical and Micro Analytical Services Pty Ltd, Melbourne or by the University of Otago, Chemistry Department, Dunedin, New Zealand. NMR spectra were recorded on a Bruker AM-300 spectrometer operating at 300 (^{1}H) and 75 (^{13}C) MHz, on a Varian Mercury 300 spectrometer operating at 300 (^{1}H) and 75 (^{13}C) MHz, or on a Bruker DRX-400 spectrometer operating at 400 (^{1}H) and 100 (^{13}C) MHz using Me_4Si (^{1}H) or the solvent peak (^{13}C) as the reference. Infrared spectra were recorded on a Perkin–Elmer 1600 FT-IR spectrophotometer. Low resolution electrospray ionisation (ESI) were recorded in the positive mode (ESI^+) on a Micromass Platform spectrometer (QMS—quadrupole mass electroscopy). Accurate mass measurements were obtained at high resolution with a Bruker BioApex 47e FTMS and a 4.7 T superconducting magnet. The instrument was externally calibrated with FC5311. Flash column chromatography was carried out using 40–63 μm (230–400 mesh) silica gel 60 (Merck no. 9385). Analytical thin layer chromatography (TLC) was performed on Polygram Sil G/UV_{254} plates. Optical rotations were measured with PolAAR 2001 polarimeter (in a cell length of 1 dm) at a wavelength of 589 nm (sodium D line) at a temperature of 22 °C. High-performance liquid chromatography (HPLC) was performed on a Varian LC Model 5000 instrument with a Waters Model 480 detector. Product distributions were obtained from peak areas from a peak printout using HP Chemstation 3365 Series II software. Chiral Daicel columns (Chiralcel OB and Chiralcel OJ) were used to assess enantiomeric excess. Both the OB and OJ columns have a cellulose ester derivative coated on silica gel adsorbent and are 0.46 cm ID × 25 cm with a particle size of 10 μm. Retention times (t_R) are an average of two runs. Analytical gas chromatography (GC) was performed on a chiral column Model CP7502 (column: 0.25 mm × 25 m, 50 CP Chiralsil-DEX CB) operated isothermally at 140 °C for 20 min using helium as the carrier gas.

Solvents were purified according to standard procedures. Chloroform used for optical rotations was of analytical purity. (+)-1,2-Bis[(2*S*,5*S*)-2,5-diethylphospholano]benzene(1,5-cyclooctadiene)rhodium(I) trifluoromethane sulfonate [(*S*,*S*)-Et–DuPHOS–Rh(I)], (−)-1,2-bis[(2*R*,5*R*)-2,5-diethylphospholano]benzene(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate [(*R*,*R*)-Et–DuPHOS–Rh(I)], (+)-1,2-bis[(2*S*,5*S*)-2,5-dimethylphospholano]benzene(1,5-cyclooctadiene)rhodium(I) trifluoromethane sulfonate [(*S*,*S*)-Me–DuPHOS–Rh(I)], (−)-1,2-bis[(2*R*,5*R*)-2,5-dimethylphospholano]benzene(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate [(*R*,*R*)-Me–DuPHOS–Rh(I)], and (+)-1,2-bis[(2*R*,5*R*)-2,5-di methylphospholano]ethane(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate [(*R*,*R*)-Me–BPE–Rh(I)] were used as supplied by Strem chemicals. Palladium on charcoal (10% Pd/C) was obtained from Aldrich. Chemical reagents were purchased from Sigma–Aldrich and were used without further purification. Argon and hydrogen (supplied by BOC gases) were of high purity (<10 ppm oxygen) and additional purification was achieved by passage of the gases through water, oxygen and hydrocarbon traps. Solvents used for metal-catalysed hydrogenation reactions were degassed with high purity nitrogen prior to use.

4.2. Preparation of formyl esters 3

4.2.1. Ethyl 3-oxo-2-phenylpropanoate 3a. Formyl ester **3a** was prepared as described by Marx et al.[65] from ester **2a** (5.85 g, 35.6 mmol) as an orange oil (2.39 g, 35%). ^{1}H NMR (300 MHz, $CDCl_3$) showed a 1:5 mixture of aldo–enol tautomers. Aldo tautomer: δ 1.29 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 4.29 (q, 2H, J = 7.1 Hz, OCH_2CH_3), 4.48 (d, 1H, J = 3.0 Hz, H2), 7.25–7.32 (m, 5H, ArC*H*), 9.78 (d, 1H, J = 3.0 Hz, H3); Enol tautomer: δ 1.29 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 4.29 (q, 2H, J = 7.1 Hz, OCH_2CH_3), 7.25–7.32 (m, 6H, ArC*H*, H3), 12.14 (d, 1H, J = 12.6 Hz, O*H*).

4.2.2. Ethyl 2-formyl-3-methylbutanoate 3b. Formyl ester **3b** was prepared according to a modified procedure of Klioze and Darmory[66] from ester **2b** (7.00 g, 48.5 mmol) as a colourless oil (4.60 g, 58%); bp 150–155 °C (30 mmHg), lit.[65] 57–59 °C (0.3 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$) showed a 1:1 mixture of aldo–enol tautomers. Aldo tautomer: δ 1.02 (d, 6H, J = 6.7 Hz, $(CH_3)_2CH$), 1.29 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 2.36–2.50 (m, 1H, H3), 2.97 (dd, 1H, J = 7.2, 2.4 Hz, H2), 4.25 (q, 2H, J = 7.2 Hz, OCH_2CH_3), 9.71 (d, 1H, J = 2.6 Hz, C*H*O); Enol tautomer: δ 1.09 (d, 6H, J = 6.8 Hz, $(CH_3)_2CH$), 1.33 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 2.57–2.63 (m, 1H, H3), 4.25 (q, 2H, J = 7.2 Hz, OCH_2CH_3), 7.03 (d, 1H, J = 12.4 Hz, C*H*═), 11.65 (d, 1H, J = 12.4 Hz, O*H*).

4.2.3. Ethyl 2-formylpropanoate 3c. Formyl ester **3c** was prepared as described by Marx et al.[65] from ester **2c** (102 g, 1.00 mol) as a colourless oil (24.0 g, 18%); bp 125–128 °C (30 mmHg), lit.[65] 42–45 °C (1.5 mmHg). ^{1}H NMR (300 MHz, $CDCl_3$) showed a 1:1 mixture of aldo–enol tautomers. Aldo tautomer: δ 1.31 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 1.36 (d, 3H, J = 7.2 Hz, H3),

3.39 (qd, 1H, $J = 7.2$, 1.4 Hz, H2), 4.25 (q, 2H, $J = 7.1$ Hz, OCH_2CH$_3$), 9.79 (d, 1H, $J = 1.2$ Hz, C*H*O); Enol tautomer: δ 1.32 (t, 3H, $J = 7.1$ Hz, OCH$_2$CH_3), 1.68 (d, 3H, $J = 1.2$ Hz, H3), 4.25 (q, 2H, $J = 7.1$ Hz, OCH_2CH$_3$), 7.00 (apparent dd, 1H, $J = 12.5$, 1.1 Hz, C*H*=), 11.33 (d, 1H, $J = 12.6$ Hz, O*H*).

4.2.4. Ethyl 2-formyl-4-methylpentanoate 3d. Formyl ester **3d** was prepared as described by Klioze and Darmory[66] from ester **2d** (7.20 g, 50.0 mmol) as a colourless oil (4.99 g, 58%); bp 85–92 °C (30 mmHg). ^{1}H NMR (300 MHz, CDCl$_3$) showed a 1:3 mixture of aldo–enol tautomers. Aldo tautomer: δ 0.83 (d, 6H, $J = 6.6$ Hz, (CH_3)$_2$CH), 1.27 (t, 3H, $J = 7.1$ Hz, OCH$_2$CH_3), 1.48–1.79 (m, 3H, H3,4), 3.33 (td, 1H, $J = 7.2$, 2.6 Hz, H2), 4.21 (q, 2H, $J = 7.1$ Hz, OCH_2CH$_3$), 9.65 (d, 1H, $J = 2.7$ Hz, C*H*O); Enol tautomer: δ 0.89 (d, 6H, $J = 6.0$ Hz, (CH_3)$_2$CH), 1.29 (t, 3H, $J = 7.2$ Hz, OCH$_2$CH_3), 1.48–1.79 (m, 1H, H4), 1.89 (d, 2H, $J = 7.2$ Hz, H3), 4.22 (q, 2H, $J = 7.1$ Hz, OCH_2CH$_3$), 6.95 (d, 1H, $J = 11.7$ Hz, C*H*=), 11.49 (d, 1H, $J = 12.3$ Hz, O*H*).

4.2.5. Ethyl 2-methyl-3-oxobutanoate 5. Sodium hydride (2.03 g, 84.5 mmol) was added to a solution of ethyl acetoacetate (10.0 g, 76.8 mmol) in anhydrous THF (80 mL) and the solution left to stir for 15 min. Methyl iodide (5.26 mL, 84.5 mmol) was then added and the reaction mixture gently heated (35–50 °C) for 16 h. Water (80 mL) was then added and the solvent evaporated under reduced pressure. The residual oil was extracted into ethyl acetate (3×100 mL) and the combined organic extract dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was distilled to afford a pale yellow oil (8.71 g, 79%); bp 83–85 °C (21 mmHg), lit.[67] 75–76 °C (15 mmHg); ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.28 (t, 3H, $J = 7.2$ Hz, OCH$_2$CH_3), 1.34 (d, 3H, $J = 7.2$ Hz, CH_3CH), 2.25 (s, 3H, H4), 3.51 (q, 1H, $J = 7.1$ Hz, H2), 4.20 (q, 2H, $J = 7.2$ Hz, OCH_2CH$_3$).

4.3. Synthesis of hydrogenation substrates 1

A mixture of formyl ester **3**, acetamide (10 equiv) and a catalytic amount of *para*-toluenesulfonic acid in toluene was heated at reflux with a Dean–Stark apparatus under a nitrogen atmosphere for 24 h. At the end of the reaction period, the reaction mixture was allowed to cool to room temperature and the excess acetamide filtered and thoroughly washed with toluene. The filtrate was evaporated under reduced pressure to give an isomeric mixture of the enamide **1**. Purification by flash chromatography furnished pure (*Z*)- and (*E*)-isomers of the desired enamide.

4.3.1. Ethyl 3-*N*-acetylamino-2-phenyl-2-propenoate 1a. Prepared from formyl ester **3a** (5.02 g, 26.0 mmol), acetamide (12.3 g, 0.21 mol) and a catalytic amount of *para*-toluenesulfonic acid in toluene (100 mL). Purification by flash chromatography on silica gel using light petroleum and ethyl acetate (4:1) first gave the (*Z*)-enamide ***Z*-1a** as a yellow-brown oil (0.75 g, 12%). IR (neat): $\nu = 2982$, 2360, 2342, 1717, 1679, 1617, 1466, 1390, 1371, 1339, 1280, 1192, 1028, 992, 911, 837, 795, 732, 700, 668, 648 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.29 (t, 3H, $J = 7.2$ Hz, OCH$_2$CH_3), 2.20 (s, 3H, CH_3CO), 4.26 (q, 2H, $J = 7.2$ Hz, OCH_2CH$_3$), 7.28–7.34 (m, 5H, Ar*H*), 7.62 (d, 1H, $J = 11.4$ Hz, H3), 10.75 (br d, 1H, $J = 11.1$ Hz, N*H*); ^{13}C NMR (75 MHz, CDCl$_3$): δ 14.4 (OCH$_2$*C*H$_3$), 16.2 (*C*H$_3$CO), 60.7 (O*C*H$_2$CH$_3$), 105.7 (C2), 127.7, 128.9, 132.7 (Ar*C*H), 132.8 (C1′), 135.4 (C3), 164.5, 170.2 (C1, *C*ONH); HRMS (ESI$^+$, MeOH): *m*/*z* calcd for $C_{13}H_{15}NO_3Na$: 256.0950. Found: 256.0937; $C_{13}H_{15}NO_3$ (233.26) calcd: C, 66.97; H, 6.48; N, 6.00. Found: C, 66.76; H, 6.44; N, 5.72. The (*E*)-isomer ***E*-1a** was then eluted and isolated as an off-white solid (1.40 g, 23%); mp 80–82 °C; IR (KBr): $\nu = 3028$, 2983, 2360, 1698, 1633, 1486, 1369, 1237, 1150, 1095, 1056, 991, 960, 931, 869, 846, 780, 737, 700 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.29 (t, 3H, $J = 7.2$ Hz, OCH$_2$CH_3), 2.02 (s, 3H, CH_3CO), 4.23 (q, 2H, $J = 7.1$ Hz, OCH_2CH$_3$), 7.23–7.48 (m, 6H, Ar*H*, N*H*), 8.24 (d, 1H, $J = 12.0$ Hz, H3); ^{13}C NMR (75 MHz, CDCl$_3$): δ 14.4 (OCH$_2$*C*H$_3$), 23.6 (*C*H$_3$CO), 60.8 (O*C*H$_2$CH$_3$), 114.2 (C2), 128.3, 129.2, 129.9 (Ar*C*H), 132.7 (C3), 133.0 (C1′), 167.0, 167.7 (C1, *C*ONH); HRMS (ESI$^+$, MeOH): *m*/*z* calcd for $C_{13}H_{15}NO_3Na$: 256.0950. Found: 256.0948; $C_{13}H_{15}NO_3$ (233.26) calcd: C, 66.97; H, 6.48; N, 6.00. Found: C, 66.75; H, 6.51; N, 5.99.

4.3.2. Ethyl 3-*N*-acetylamino-2-isopropyl-2-propenoate 1b. Prepared from formyl ester **3b** (5.80 g, 36.7 mmol), acetamide (21.7 g, 0.37 mol) and a catalytic amount of *para*-toluenesulfonic acid in toluene (100 mL). Purification by flash chromatography on silica gel using light petroleum, dichloromethane and ethyl acetate (4:1:1) first gave the (*Z*)-enamide ***Z*-1b** as a yellow-brown oil (1.30 g, 19%). IR (neat): $\nu = 2963$, 2873, 2360, 1715, 1681, 1625, 1478, 1373, 1303, 1270, 1195, 1180, 1122, 1094, 1058, 1030, 989, 937, 834, 794, 720, 669 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.11 (d, 6H, $J = 6.9$ Hz, (CH_3)$_2$CH), 1.33 (t, 3H, $J = 7.1$ Hz, OCH$_2$CH_3), 2.14 (s, 3H, CH_3CO), 2.71–2.84 (m, 1H, (CH$_3$)$_2$C*H*), 4.24 (q, 2H, $J = 7.1$ Hz, OCH_2CH$_3$), 7.39 (dd, 1H, $J = 11.0$, 0.8 Hz, H3), 10.57 (br d, 1H, $J = 7.2$ Hz, N*H*); ^{13}C NMR (75 MHz, CDCl$_3$): δ 14.2 (OCH$_2$*C*H$_3$), 22.5 ((*C*H$_3$)$_2$CH), 23.7 (*C*H$_3$CO), 28.1 ((CH$_3$)$_2$*C*H), 60.4 (O*C*H$_2$CH$_3$), 115.4 (C2), 133.2 (C3), 168.3, 169.5 (C1, *C*ONH); HRMS (ESI$^+$, MeOH): *m*/*z* calcd for $C_{10}H_{17}NO_3Na$: 222.1106. Found: 222.1095; $C_{10}H_{17}NO_3$ (199.25) calcd: C, 60.26; H, 8.60; N, 7.03. Found: C, 60.27; H, 8.58; N, 6.98. The (*E*)-isomer ***E*-1b** was then eluted and isolated as a colourless solid (1.50 g, 23%); mp 109–110 °C; IR (KBr): $\nu = 2977$, 1704, 1633, 1496, 1371, 1252, 1143, 1042, 1001, 958, 939, 872, 778, 708, 606, 572, 529 cm^{-1}; ^{1}H NMR. (300 MHz, CDCl$_3$): δ 1.24 (d, 6H, $J = 6.9$ Hz, (CH_3)$_2$CH), 1.29 (t, 3H, $J = 7.1$ Hz, OCH$_2$CH_3), 2.16 (s, 3H, CH_3CO), 2.70 (h, 1H, $J = 7.0$ Hz, (CH$_3$)$_2$C*H*), 4.18 (q, 2H, $J = 7.1$ Hz, OCH_2CH$_3$), 7.27 (br d, 1H, J obscured by CDCl$_3$ peak, N*H*), 7.91 (d, 1H, $J = 12.3$ Hz, H3); ^{13}C NMR (75 MHz, CDCl$_3$): δ 14.4 (OCH$_2$*C*H$_3$), 20.8 ((*C*H$_3$)$_2$CH), 23.7 (*C*H$_3$CO), 26.6 ((CH$_3$)$_2$*C*H), 60.1 (O*C*H$_2$CH$_3$), 117.9 (C2), 130.4 (C3),

167.5, 168.0 (C1, *C*ONH); HRMS (ESI^+, MeOH): *m/z* calcd for $C_{10}H_{17}NO_3Na$: 222.1106. Found: 222.1103; $C_{10}H_{17}NO_3$ (199.25) calcd: C, 60.26; H, 8.60; N, 7.03. Found: C, 60.13; H, 8.88; N, 6.95.

4.3.3. Ethyl 3-*N*-acetylamino-2-methyl-2-propenoate 1c. Prepared from formyl ester **3c** (1.09 g, 8.38 mmol), acetamide (5.00 g, 84.6 mmol) and a catalytic amount of *para*-toluenesulfonic acid in toluene (12 mL). Purification by flash chromatography on silica gel using light petroleum and ethyl acetate (1:1) first gave the (*Z*)-enamide ***Z*-1c** as an off-white waxy solid (0.20 g, 14%); mp 42–43 °C; IR (KBr): ν = 2980, 2978, 1706, 1682, 1624, 1489, 1439, 1394, 1370, 1342, 1273, 1224, 1194, 1160, 1112, 1031, 982, 946, 859, 780, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 1.84 (d, 3H, J = 1.5 Hz, CH_3C=), 2.13 (s, 3H, CH_3CO), 4.22 (q, 2H, J = 7.2 Hz, OCH_2CH_3), 7.37 (dq, 1H, J = 11.2, 1.3 Hz, H3), 10.40 (br s, 1H, N*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3 (OCH_2CH_3), 16.1 (CH_3C=), 23.8 (CH_3CO); 60.5 (OCH_2CH_3), 104.7 (C2), 134.8 (C3), 168.2, 169.8 (C1, *C*ONH); HRMS (ESI^+, MeOH): *m/z* calcd for $C_8H_{13}NO_3Na$: 194.0793. Found: 194.0789; $C_8H_{13}NO_3$ (171.19) calcd: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.35; H, 7.67; N, 7.88. The (*E*)-isomer ***E*-1c** was then eluted and isolated as an off-white solid (0.61 g, 43%); mp 114–116 °C; IR (KBr): ν = 2992, 1712, 1667, 1631, 1528, 1476, 1397, 1366, 1335, 1272, 1208, 1138, 1032, 987, 970, 886, 853, 694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.29 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 1.82 (d, 3H, J = 1.5 Hz, CH_3C=), 2.18 (s, 3H, CH_3CO), 4.20 (q, 2H, J = 7.1 Hz, OCH_2CH_3), 7.20 (br d, 1H, J = 9.9 Hz, N*H*), 8.00 (apparent dd, 1H, J = 12.0, 1.5 Hz, H3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.7 (CH_3C=), 14.4 (OCH_2CH_3), 23.5 (CH_3CO), 60.6 (OCH_2CH_3), 108.0 (C2), 131.8 (C3), 168.2, 168.4 (C1, *C*ONH); HRMS (ESI^+, MeOH): *m/z* calcd for $C_8H_{13}NO_3Na$: 194.0793. Found: 194.0787.

4.3.4. Ethyl 3-*N*-acetylamino-2-isobutyl-2-propenoate 1d. Prepared from formyl ester **3d** (1.00 g, 5.81 mmol), acetamide (3.50 g, 59.2 mmol) and a catalytic amount of *para*-toluenesulfonic acid in toluene (30 mL). Purification by flash chromatography on silica gel using light petroleum, dichloromethane and ethyl acetate (4:1:1) first gave the (*Z*)-enamide ***Z*-1d** as a brown oil (0.10 g, 8%); IR (neat): ν = 2958, 2870, 2360, 1716, 1682, 1628, 1467, 1372, 1346, 1290, 1269, 1188, 1095, 1031, 933, 822, 786 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.86 (d, 6H, J = 6.6 Hz, $(CH_3)_2CH$), 1.31 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 1.67–1.80 (m, 1H, $(CH_3)_2CH$), 2.06 (d, 2H, J = 7.0, Hz, CH_2C=), 2.14 (s, 3H, CH_3CO), 4.21 (q, 2H, J = 7.1 Hz, OCH_2CH_3), 7.32 (d, 1H, J = 11.1 Hz, H3), 10.48 (br d, 1H, J = 9.9 Hz, N*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3 (OCH_2CH_3), 22.3 ($(CH_3)_2CH$), 23.8 (CH_3CO), 28.3 ($(CH_3)_2CH$), 39.5 (CH_2C=), 60.4 (OCH_2CH_3), 108.4 (C2), 135.7 (C3), 168.4, 169.8 (C1, *C*ONH); HRMS (ESI^+, MeOH): *m/z* calcd for $C_{11}H_{19}NO_3Na$: 236.1263. Found: 236.1261; $C_{11}H_{19}NO_3$ (213.27) calcd: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.91; H, 8.90; N, 6.28. The (*E*)-isomer ***E*-1d** was then eluted and isolated as a brown oil (0.48 g, 39%); IR (neat): ν = 2960, 2871, 2358, 1694, 1645, 1506, 1469, 1369, 1279, 1228, 1170, 1136, 1086, 913, 822, 765, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.92 (d, 6H, J = 6.6 Hz, $(CH_3)_2CH$), 1.29 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 1.76–1.86 (m, 1H, $(CH_3)_2CH$), 2.13 (d, 2H, J = 7.2 Hz, CH_2C=), 2.16 (s, 3H, CH_3CO), 4.19 (q, 2H, J = 7.1 Hz, OCH_2CH_3), 7.24 (br d, 1H, J = 11.1 Hz, N*H*), 8.06 (d, 1H, J = 12.0 Hz, H3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4 (OCH_2CH_3), 22.5 ($(CH_3)_2CH$), 23.6 (CH_3CO), 28.2 ($(CH_3)_2CH$), 34.5 (CH_2C=), 60.5 (OCH_2CH_3), 112.3 (C2), 132.1 (C3), 168.0, 168.3 (C1, *C*ONH); HRMS (ESI^+, MeOH): *m/z* calcd for $C_{11}H_{19}NO_3Na$: 236.1263. Found: 236.1257.

4.3.5. Ethyl 3-*N*-benzoylamino-2-methyl-2-propenoate. Prepared from formyl ester **3c** (1.59 g, 12.2 mmol), benzamide (4.47 g, 36.9 mmol) and a catalytic amount of *para*-toluenesulfonic acid in toluene (70 mL). Purification by flash chromatography on silica gel using light petroleum and ethyl acetate (2:1) first gave the title (*Z*)-enamide as an off-white waxy solid (2.41 g, 85%); mp 65–66 °C; IR (KBr): ν = 3067, 2981, 2252, 1682, 1633, 1582, 1505, 1480, 1453, 1440, 1393, 1371, 1338, 1278, 1235, 1201, 1150, 1095, 1069, 1028, 912, 868, 844, 800, 780, 734, 700, 676, 648 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.35 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 1.92 (d, 3H, J = 1.2 Hz, CH_3C=), 4.27 (q, 2H, J = 7.1 Hz, OCH_2CH_3), 7.46–7.59 (m, 3H, H3′, 4′, 5′), 7.61–7.65 (m, 1H, H3), 7.93–7.96 (m, 2H, H2′, 6′), 11.47 (br d, 1H, J = 10.5 Hz, N*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4 (OCH_2CH_3), 16.2 (CH_3C=), 60.7 (OCH_2CH_3), 105.7 (C2), 127.7, 128.9, 132.7 (Ar*C*H), 132.8 (C1′), 135.4 (C3), 164.5, 170.1 (C1, *C*ONH); HRMS (ESI^+, MeOH): *m/z* calcd for $C_{13}H_{15}NO_3Na$: 256.0950. Found: 256.0939; $C_{13}H_{15}NO_3$ (233.11) calcd: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.16; H, 6.42; N, 5.95. The title (*E*)-isomer was then eluted and isolated as an off-white solid (0.26 g, 9%); mp 89–91 °C; IR (KBr): ν = 3178, 2978, 2363, 1703, 1646, 1579, 1560, 1515, 1482, 1450, 1395, 1368, 1353, 1264, 1208, 1184, 1138, 1074, 1041, 1027, 1001, 922, 902, 875, 798, 754, 702, 654, 636 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 1.93 (d, 3H, J = 1.5 Hz, CH_3C=), 4.24 (q, 2H, J = 7.2 Hz, OCH_2CH_3), 7.49–7.53 (m, 2H, H3′, 5′), 7.58–7.64 (m, 1H, H4′), 7.80 (br d, 1H, J = 12.0 Hz, N*H*), 7.83–7.87 (m, 2H, H2′, 6′), 8.23 (apparent dd, 1H, J = 12.0, 1.2 Hz, H3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.9 (CH_3C=), 14.5 (OCH_2CH_3), 60.7 (OCH_2CH_3), 100.1 (C2), 127.4, 129.2, 132.0, 132.9 (Ar*C*H, C3), 133.0 (C1′), 162.3, 168.3 (C1, *C*ONH); HRMS (ESI^+, MeOH): *m/z* calcd for $C_{13}H_{15}NO_3Na$: 256.0950. Found: 256.0943; $C_{13}H_{15}NO_3$ (233.11) calcd: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.14; H, 6.26; N, 5.99.

4.3.6. (2*Z*)-Ethyl 3-*N*-acetylamino-2-methyl-2-butenoate *Z*-4. Prepared from ketoester **5** (2.08 g, 74.4 mmol), acetamide (2.56 g, 43.3 mmol) and a catalytic amount of *para*-toluenesulfonic acid in toluene (20 mL). Purification by flash chromatography on silica gel using light petroleum and ethyl acetate (2:1) gave the (*Z*)-enamide ***Z*-4** as a yellow oil (0.84 g, 32%); IR (neat): ν = 3059, 2982, 2360, 1728, 1660, 1548, 1454, 1373, 1266, 1225,

1194, 1164, 1032, 862, 738, 702, 639 cm^{-1}; ^1H NMR. (400 MHz, $CDCl_3$): δ 1.31 (t, 3H, $J = 7.1$ Hz, OCH_2CH_3), 1.83 (q, 3H, $J = 0.8$ Hz, H4), 2.11 (s, 3H, CH_3CO), 2.41 (q, 3H, $J = 0.8$ Hz, $CH_3C{=}$), 4.19 (q, 2H, $J = 7.1$ Hz, OCH_2CH_3), 11.61 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.6 (C4), 14.3 (OCH_2CH_3), 17.3 ($CH_3C{=}$), 25.5 (CH_3CO), 60.4 (OCH_2CH_3), 103.2 (C2), 150.3 (C3), 169.0, 170.2 (C1, CONH); MS (ESI^+, H_2O/MeCN): *m/z* 186.2 [$(M+H)^+$]. Spectral data consistent with that previously reported.[61]

4.3.7. (2*E*)-Ethyl 3-*N*-acetylamino-2-methyl-2-butenoate *E*-4. A solution of (2*Z*)-ethyl 3*N*-acetylamino-2-methyl-2-butenoate ***Z*-4** (0.50 g, 2.70 mmol) in toluene was irradiated with ultraviolet light in a Hanovia photochemical reactor operating at 125 W using a medium-pressure mercury arc lamp. An internal condenser was used to maintain the reaction temperature between 10 and 20 °C. After 7 h, the reaction mixture was evaporated under reduced pressure to afford the (*E*)-enamide (0.49 g, 98%) ***E*-4** as an off-white waxy solid, mp 38–40 °C. IR (neat): $\nu = 3253$, 2996, 2368, 1705, 1690, 1560, 1518, 1474, 1372, 1292, 1268, 1235, 1110, 1032, 950, 870, 770, 746, 648, 606, 468, 420 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, 3H, $J = 7.1$ Hz, OCH_2CH_3), 1.76 (d, 3H, $J = 1.4$ Hz, H4), 2.02 (s, 3H, CH_3CO), 2.28 (d, 3H, $J = 1.4$ Hz, $CH_3C{=}$), 4.12 (q, 2H, $J = 7.1$ Hz, OCH_2CH_3), 6.99 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3 (OCH_2CH_3), 14.6 (C4), 19.4 ($CH_3C{=}$), 24.1 (CH_3CO), 60.5 (OCH_2CH_3), 101.4 (C2), 142.6 (C3), 168.4, 168.8 (C1, CONH); HRMS (ESI^+, MeOH): *m/z* calcd for $C_9H_{15}NO_3Na$: 208.0950. Found: 208.0942.

4.4. Hydrogenation reactions

Method 1: Reactions employing Pd/C were performed in a Fischer–Porter shielded aerosol pressure reactor that was charged with catalyst (5–10 mg), substrate (30–200 mg) and solvent (5–10 mL). The reaction vessel was connected to the hydrogenation manifold and evacuated and flushed with argon gas before being charged with hydrogen gas (90 psi). The reaction was stirred at ambient temperature for 72 h. The hydrogen gas was vented, the catalyst removed via filtration through a Celite pad and the solvent removed in vacuo.

Method 2: Reactions involving the asymmetric homogeneous catalysts (Rh(I) complexes of DuPHOS and BPE) were performed using a drybox. In the drybox, a Fischer–Porter shielded aerosol pressure reactor was charged with catalyst (1–3 mg), substrate 25–52 mg and dry deoxygenated solvent (4–10 mL). For liquid substrates, a freeze–pump–thaw cycle was applied. The reaction vessel was assembled and tightly sealed within the drybox. The apparatus was connected to the hydrogenation manifold and purged three times using a vacuum and argon flushing cycle before being pressurised with hydrogen gas. The reaction was then stirred at the reported temperature for the reported reaction time. The hydrogen gas was vented and the solvent was removed in vacuo. Purification was achieved by flash chromatography (silica, ethyl acetate).

Hydrogenation experiments are described in the following format: substrate, solvent, catalyst, hydrogen pressure, reaction temperature, reaction time, isolated yield, retention time (GC/HPLC conditions) and enantiomeric excess.

4.4.1. Ethyl 3-*N*-acetylamino-2-phenylpropanoate 6a. (a) (2*E*)-Ethyl 3-*N*-acetylamino-2-phenyl-2-propenoate ***E*-1a** (30.0 mg, 0.13 mmol), ethanol (7 mL), Pd/C (5 mg) using Method 1 gave **6a**, yield 96%, HPLC: $t_R = 8.8$ and 12.5 min, Chiralcel OJ, flow rate = 1.0 mL min^{-1}, detection at 254 nm, eluent = 90% hexane–10% 2-propanol. (b) (2*E*)-Ethyl 3-*N*-acetylamino-2-phenyl-2-propenoate ***E*-1a** (47.0 mg, 0.20 mmol), methanol (8 mL), (*R*,*R*)-Me–BPE–Rh(I) (3 mg), 60 psi H_2, 20 °C, 72 h using Method 2 gave **6a**, yield 91%, HPLC: $t_R = 9.8$ and 13.5 min, 67% ee. (c) (2*E*)-Ethyl 3-*N*-acetylamino-2-phenyl-2-propenoate ***E*-1a** (46.0 mg, 0.20 mmol), methanol (8 mL), (*S*,*S*)-Me–DuPHOS–Rh(I) (3 mg), 90 psi H_2, 50 °C, 24 h using Method 2 gave **6a**, yield 100%, HPLC: $t_R = 9.4$ and 12.7 min, 47% ee. (d) (2*E*)-Ethyl 3-*N*-acetylamino-2-phenyl-2-propenoate ***E*-1a** (40.0 mg, 0.17 mmol), methanol (7 mL), (*S*,*S*)-Et–DuPHOS–Rh(I) (3 mg), 90 psi H_2, 50 °C, 72 h using Method 2 gave **6a**, yield 98%, HPLC: $t_R = 9.3$ and 12.5 min, 26% ee. (e) (2*E*)-Ethyl 3-*N*-acetylamino-2-phenyl-2-propenoate ***E*-1a** (26.8 mg, 0.11 mmol), benzene (5 mL), (*R*,*R*)-Me–BPE–Rh(I) (2 mg), 90 psi H_2, 50 °C, 24 h using Method 2 gave **6a**, yield 95%, HPLC: $t_R = 9.3$ and 13.1 min, 5% ee. (f) (2*E*)-Ethyl 3-*N*-acetylamino-2-phenyl-2-propenoate ***E*-1a** (40.0 mg, 0.17 mmol), benzene (9 mL), (*S*,*S*)-Et–DuPHOS–Rh(I) (3 mg), 90 psi H_2, 50 °C, 72 h using Method 2 gave **6a**, yield 72% (28% recovered ***E*-1a**), HPLC: $t_R = 9.2$ and 13.0 min, 33% ee. (g) (2*Z*)-Ethyl 3-*N*-acetylamino-2-phenyl-2-propenoate ***Z*-1a** (28.0 mg, 0.12 mmol), methanol (6 mL), (*R*,*R*)-Me–BPE–Rh(I) (2 mg), 90 psi H_2, 50 °C, 72 h using Method 2 gave **6a**, yield 96%, HPLC: $t_R = 9.8$ and 13.2 min, 14% ee.

Compound **6a**: Colourless oil; IR (neat): $\nu = 3068$, 2983, 2935, 2361, 1731, 1652, 1556, 1496, 1455, 1371, 1282, 1199, 1177, 1097, 1064, 1030, 860, 736, 700 cm^{-1}; ^1H NMR. (400 MHz, $CDCl_3$): δ 1.20 (t, 3H, $J = 7.1$ Hz, OCH_2CH_3), 1.93 (s, 3H, CH_3CO), 3.60–3.71 (m, 2H, H3), 3.88 (dd, 1H, $J = 8.8$, 6.0 Hz, H2), 4.09–4.22 (m, 2H, OCH_2CH_3), 5.86 (br s, 1H, NH), 7.22–7.35 (m, 5H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2 (OCH_2CH_3), 23.4 (CH_3CO), 42.4 (C3), 51.3 (C2), 61.3 (OCH_2CH_3), 127.9, 128.1, 129.0 (ArCH), 136.6 (C1′), 170.5, 173.2 (C1, CONH); MS (ESI^+, H_2O/MeOH): *m/z* 236.1 [$(M+H)^+$]. ^1H NMR spectral data for **6a** was consistent with that previously reported.[68]

A solution of ethyl 3-*N*-acetylamino-2-phenylpropanoate **6a** (Sample 4.4.1 b) (23.0 mg, 0.10 mmol) in 6 M HCl (6 mL) was heated at reflux for 7 h. The reaction mixture was then evaporated under reduced pressure to afford 3-amino-2-phenylpropanoic acid hydrochloride salt, as a pale yellow oil (19.1 mg, 97 %); ^1H NMR (300 MHz, CD_3OD): δ 3.21 (dd, 1H, $J = 12.9$, 6.0 Hz, $H3_A$), 3.55 (dd, 1H, $J = 12.5$, 9.1 Hz, $H3_B$), 4.00 (dd, 1H, $J = 9.0$, 6.0 Hz, H2), 7.28–7.44 (m, 5H,

Ar*H*); $[\alpha]_D$ = +59.9 (*c* 0.95, H_2O), {lit.[69] for (*R*) $[\alpha]_D$ = +85 (*c* 0.2, H_2O)}.

4.4.2. Ethyl 3-*N*-acetylamino-2-isopropylpropanoate 6b. (a) (2*E*)-Ethyl 3-*N*-acetylamino-2-isopropyl-2-propenoate ***E*-1b** (206 mg, 1.20 mmol), ethanol (10 mL), Pd/C (10 mg) using Method 1 gave **6b**, yield 94%, HPLC: t_R = 24.9 and 33.1 min, Chiralcel OB, flow rate = 1.0 mL min^{-1}, detection at 220 nm, eluent = 98% hexane–2% 2-propanol. (b) (2*E*)-Ethyl 3-*N*-acetylamino-2-isopropyl-2-propenoate ***E*-1b** (25.5 mg, 0.13 mmol), methanol (4 mL), (*R*,*R*)-Me–BPE–Rh(I) (2 mg), 60 psi H_2, 20 °C, 72 h using Method 2 gave **6b**, yield 93%, HPLC: t_R = 24.7 and 30.2 min, 67% ee. (c) (2*E*)-Ethyl 3-*N*-acetylamino-2-isopropyl-2-propenoate ***E*-1b** (25.0 mg, 0.13 mmol), methanol (4 mL), (*R*,*R*)-Et–DuPHOS–Rh(I) (2 mg), 60 psi H_2, 20 °C, 72 h using Method 2 gave **6b**, yield 93%, HPLC: t_R = 22.2 and 28.6 min, 58% ee. (d) (2*E*)-Ethyl 3-*N*-acetylamino-2-isopropyl-2-propenoate ***E*-1b** (47.0 mg, 0.24 mmol), benzene (5 mL), (*R*,*R*)-Me–BPE–Rh(I) (3 mg), 90 psi H_2, 20 °C, 72 h using Method 2 gave **6b**, yield 95%, HPLC: t_R = 24.3 and 33.8 min, 32% ee. (e) (2*E*)-Ethyl 3-*N*-acetylamino-2-isopropyl-2-propenoate ***E*-1b** (26.0 mg, 0.13 mmol), benzene (5 mL), (*R*,*R*)-Me–DuPHOS–Rh(I) (2 mg), 90 psi H_2, 50 °C, 72 h using Method 2 gave **6b**, yield 92%, HPLC: t_R = 25.7 and 33.5 min, 23% ee. (f) (2*E*)-Ethyl 3-*N*-acetylamino-2-isopropyl-2-propenoate ***E*-1b** (26.0 mg, 0.13 mmol), benzene (5 mL), (*R*,*R*)-Et–DuPHOS–Rh(I) (2 mg), 90 psi H_2, 50 °C, 72 h using Method 2 gave **6b**, yield 88%, HPLC: t_R = 25.0 and 32.4 min, 31% ee.

Compound **6b**: Colourless oil; IR (neat): *v* = 2965, 2876, 2359, 1729, 1655, 1552, 1466, 1374, 1281, 1188, 1097, 1032, 853 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.96, 0.97 (d, 6H, *J* = 6.9 Hz, $(CH_3)_2CH$), 1.28 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3), 1.96 (s, 3H, CH_3CO), 1.97–2.06 (m, 1H, $(CH_3)_2CH$), 2.40–2.46 (m, 1H, H2), 3.33 (ddd, 1H, *J* = 15.0, 9.4, 5.8 Hz, $H3_A$), 3.58 (ddd, 1H, *J* = 13.5, 6.2, 3.8 Hz, $H3_B$), 4.09–4.26 (m, 2H, OCH_2CH_3), 5.94 (br s, 1H, N*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4 (OCH_2CH_3), 20.1, 20.3 ($(CH_3)_2CH$), 23.4 (CH_3CO), 28.8 ($(CH_3)_2CH$), 38.5 (C3), 51.6 (C2), 60.6 (OCH_2CH_3), 170.2, 175.1 (C1, *C*ONH); HRMS (ESI^+, MeOH): *m*/*z* calcd for $C_{10}H_{19}NO_3Na$: 224.1263. Found: 224.1256.

4.4.3. Ethyl 3-*N*-acetylamino-2-methylpropanoate 6c. (a) (2*E*)-Ethyl 3-*N*-acetylamino-2-methyl-2-propenoate ***E*-1c** (35.0 mg, 0.20 mmol), ethanol (7 mL), Pd/C (5 mg) using Method 1 gave **6c**, yield 99%, GC: t_R = 7.9 and 8.1 min. (b) (2*E*)-Ethyl 3-*N*-acetylamino-2-methyl-2-propenoate ***E*-1c** (52.6 mg, 0.31 mmol), methanol (7 mL), (*R*,*R*)-Me–BPE–Rh(I) (3 mg), 60 psi H_2, 20 °C, 24 h using Method 2 gave **6c**, yield 95%, GC: t_R = 7.9 and 8.1 min, 22% ee. (c) (2*E*)-Ethyl 3-*N*-acetylamino-2-methyl-2-propenoate ***E*-1c** (44.5 mg, 0.26 mmol), methanol (7 mL), (*S*,*S*)-Me–DuPHOS–Rh(I) (3 mg), 60 psi H_2, 20 °C, 24 h using Method 2 gave **6c**, yield 71% (29% recovered ***E*-1c**), GC: t_R = 7.9 and 8.1 min, 18% ee. (d) Ethyl 3-*N*-acetylamino-2-methyl-2-propenoate ***E*-1c** (51.4 mg, 0.30 mmol), methanol (7 mL), (*S*,*S*)-Et–DuPHOS–Rh(I) (3 mg), 60 psi H_2, 20 °C, 24 h using Method 2 gave **6c**, yield 96%, GC: t_R = 8.1 and 8.3 min, 8% ee. (e) (2*E*)-Ethyl 3-*N*-acetylamino-2-methyl-2-propenoate ***E*-1c** (43.5 mg, 0.25 mmol), benzene (10 mL), (*R*,*R*)-Me–BPE–Rh(I) (3 mg), 90 psi H_2, 50 °C, 72 h using Method 2 gave **6c**, yield 98%, GC: t_R = 7.9 and 8.1 min, 33% ee. (f) (2*E*)-Ethyl 3-*N*-acetylamino-2-methyl-2-propenoate ***E*-1c** (50.3 mg, 0.29 mmol), benzene (10 mL), (*R*,*R*)-Me–DuPHOS–Rh(I) (3 mg), 90 psi H_2, 50 °C, 72 h using Method 2 gave **6c**, yield 100%, GC: t_R = 8.3 and 8.5 min, 12% ee. (g) (2*E*)-Ethyl 3-*N*-acetylamino-2-methyl-2-propenoate ***E*-1c** (42.9 mg, 0.25 mmol), benzene (10 mL), (*R*,*R*)-Et–DuPHOS–Rh(I) (3 mg), 90 psi H_2, 50 °C, 72 h using Method 2 gave **6c**, yield 99%, GC: t_R = 8.3 and 8.5 min, 16% ee. (h) (2*Z*)-Ethyl 3-*N*-acetylamino-2-methyl-2-propenoate ***Z*-1c** (53.0 mg, 0.31 mmol), methanol (7 mL), (*R*,*R*)-Me–BPE–Rh(I) (3 mg), 90 psi H_2, 50 °C, 72 h using Method 2 gave **6c**, yield 94%, GC: t_R = 7.9 and 8.1 min, 11% ee.

Compound **6c**: Colourless oil; IR (neat): *v* = 3090, 2981, 2940, 1732, 1660, 1557, 1463, 1374, 1264, 1192, 1141, 1094, 1058, 1032, 928, 860, 757, 640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.18 (d, 3H, *J* = 7.2 Hz, CH_3CH), 1.28 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3), 1.97 (s, 3H, CH_3CO), 2.63–2.74 (m, 1H, H2), 3.29 (ddd, 1H, *J* = 13.8, 8.2, 5.7 Hz, $H3_A$), 3.51 (ddd, 1H, *J* = 13.8, 6.8, 4.5 Hz, $H3_B$), 4.16 (q, 2H, *J* = 7.1 Hz, OCH_2CH_3), 6.09 (br s, 1H, N*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 14.9 (OCH_2CH_3, CH_3CH), 23.3 (CH_3CO), 39.6 (C2), 41.7 (C3), 60.8 (OCH_2CH_3), 170.4, 175.7 (C1, *C*ONH); HRMS (ESI^+, MeOH): *m*/*z* calcd for $C_8H_{15}NO_3Na$: 196.0950. Found: 196.0945.

A solution of ethyl 3-*N*-acetylamino-2-methylpropanoate **6c** (Sample 4.4.3 e) (33.0 mg, 0.19 mmol) in 6 M HCl (6 mL) was heated at reflux for 7 h. The reaction mixture was then evaporated under reduced pressure to afford 3-amino-2-methylpropanoic acid hydrochloride salt, as a pale yellow oil (26.4 mg, 99%); ^1H NMR (300 MHz, CD_3OD): δ 1.27 (br s, 3H, CH_3CH), 2.81–3.15 (m, 3H, H2, 3); $[\alpha]_D$ = −5.6 (*c* 1.30, H_2O), {lit. [70] for (*S*) $[\alpha]_D$ = +14.2 (*c* 1.3, 1 M HCl)}.

4.4.4. Ethyl 3-*N*-acetylamino-2-isobutylpropanoate 6d. (a) (2*E*)-Ethyl 3-*N*-acetylamino-2-isobutyl-2-propenoate ***E*-1d** (45.0 mg, 0.21 mmol), ethanol (5 mL), Pd/C (5 mg) using Method 1 gave **6d**, yield 95%, HPLC: t_R = 11.1 and 13.2 min, Chiralcel OJ, flow rate = 1.0 mL min^{-1}, detection at 220 nm, eluent = 97% hexane–3% 2-propanol. (b) (2*E*)-Ethyl 3-*N*-acetylamino-2-isobutyl-2-propenoate ***E*-1d** (27.0 mg, 0.13 mmol), methanol (5 mL), (*R*,*R*)-Me–BPE–Rh(I) (2 mg), 60 psi H_2, 20 °C, 72 h using Method 2 gave **6d**, yield 90%, HPLC: t_R = 10.3 and 12.1 min, <5% ee. (c) (2*E*)-Ethyl 3-*N*-acetylamino-2-isobutyl-2-propenoate ***E*-1d** (36.0 mg, 0.17 mmol), methanol (5 mL), (*S*,*S*)-Me–DuPHOS–Rh(I) (3 mg), 60 psi H_2, 20 °C, 72 h using Method 2 gave **6d**, yield 98%, HPLC: t_R = 11.9 and 13.9 min, 10% ee. (d) (2*E*)-Ethyl 3-*N*-acetylamino-2-isobutyl-2-propenoate ***E*-1d** (39.0 mg, 0.18 mmol), methanol (5 mL), (*S*,*S*)-Et–DuPHOS–Rh(I) (3 mg), 60 psi H_2,

20 °C, 72 h using Method 2 gave **6d**, yield 97%, HPLC: t_R = 10.8 and 12.6 min, 14% ee.

Compound **6d**: Colourless oil; IR (neat): ν = 3058, 2860, 2872, 2360, 1732, 1659, 1556, 1469, 1371, 1268, 1186, 1127, 1040, 922, 855, 737, 703 cm^{-1}; ^1H NMR. (300 MHz, $CDCl_3$): δ 0.91 (d, J = 6.3 Hz), 0.91 (d, J = 6.6 Hz) (6H, $(CH_3)_2CH$), 1.27 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 1.49–1.68 (m, 3H, $(CH_3)_2CHCH_2$), 1.97 (s, 3H, CH_3CO), 2.64–2.72 (m, 1H, H2), 3.30 (ddd, 1H, J = 13.8, 8.2, 4.6 Hz, $H3_A$), 3.50 (ddd, 1H, J = 13.6, 6.6, 3.4 Hz, $H3_B$), 4.16 (q, 2H, J = 7.1 Hz, OCH_2CH_3), 5.93 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4 (OCH_2CH_3), 22.5, 22.7 ($(CH_3)_2CH$), 23.4 (CH_3CO), 26.0 ($(CH_3)_2CH$), 39.0, 40.8 (C3, $(CH_3)_2CHCH_2$), 43.3 (C2), 60.8 (OCH_2CH_3), 170.3, 175.8 (C1, CONH); HRMS (ESI^+, MeOH): m/z calcd for $C_{11}H_{21}NO_3Na$: 238.1419. Found: 238.1415.

4.4.5. Ethyl 3-*N*-benzoylamino-2-methylpropanoate. (a) (2*Z*)-Ethyl 3-*N*-benzoylamino-2-methyl-2-propenoate (111 mg, 0.47 mmol), ethanol (7 mL), Pd/C (10 mg) using Method 1 gave the title ester, yield 100%. (b) (2*E*)-Ethyl 3-*N*-benzoylamino-2-methyl-2-propenoate (41.5 mg, 0.18 mmol), methanol (7 mL), (*S*,*S*)-Me–DuPHOS–Rh(I) (3 mg), 90 psi H_2, 50 °C, 72 h using Method 2 gave the title ester, yield 97%, $[\alpha]_D$ = +2.9 (*c* 0.5, $CHCl_3$), (lit.[71] +3.1 (*c* 1.0, $CHCl_3$) 11% ee), 10% ee. (c) (2*E*)-Ethyl 3-*N*-benzoylamino-2-methyl-2-propenoate (41.8 mg, 0.18 mmol), methanol (7 mL), (*R*,*R*)-Me–BPE–Rh(I) (3 mg), 60 psi H_2, 20 °C, 24 h using Method 2 gave the title ester, yield 88%, $[\alpha]_D$ = −4.8 (*c* 0.4, $CHCl_3$), {lit.[71] $[\alpha]_D$ = +3.1 (*c* 1.0, $CHCl_3$) 11% ee}, 17% ee.

Ethyl 3-N-benzoylamino-2-methylpropanoate: Pale yellow oil; IR (neat): ν = 3062, 2980, 2938, 2361, 2342, 1731, 1645, 1579, 1538, 1490, 1448, 1381, 1310, 1259, 1193, 1135, 1095, 1076, 1026, 930, 861, 803, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (d, 3H, J = 7.2 Hz, CH_3CH), 1.27 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 2.75–2.87 (m, 1H, H2), 3.51 (ddd, 1H, J = 13.8, 8.2, 5.7 Hz, $H3_A$), 3.73 (ddd, 1H, J = 13.5, 6.6, 4.2 Hz, $H3_B$), 4.18 (q, 2H, J = 7.1 Hz, OCH_2CH_3), 6.82 (br s, 1H, NH), 7.40–7.51 (m, 3H, H3′, 4′, 5′), 7.76 (d, 2H, J = 6.9 Hz, H2′, 6′); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 15.1 (CH_3CH, OCH_2CH_3), 39.6 (C2), 42.1 (C3), 60.9 (OCH_2CH_3), 127.0, 128.7, 131.6 (ArCH), 134.6 (C1′), 167.6, 176.0 (C1, CONH); MS (ESI^+, H_2O/MeOH): m/z 236.1 $[(M+H)^+]$.

4.4.6. Ethyl 3-*N*-acetylamino-2-methylbutanoate 7. (a) (2*E*)-Ethyl 3-*N*-acetylamino-2-methyl-2-butenoate ***E*-4** (43.0 mg, 0.23 mmol), ethanol (8 mL), Pd/C (3 mg) using Method 1 gave **7**, yield 98%, GC: t_R = 6.4 and 6.7 min with 63.1% area combined, and 7.7 and 7.9 min with 36.9% area combined. (b) (2*E*)-Ethyl 3-*N*-acetylamino-2-methyl-2-butenoate ***E*-4** (40.0 mg, 0.22 mmol), methanol (6 mL), (*R*,*R*)-Me–BPE–Rh(I) (3 mg), 60 psi H_2, 20 °C, 72 h using Method 2 gave **7**, yield 96%, GC: t_R = 6.4 and 6.7 min, 48% ee. (c) (2*E*)-Ethyl 3-*N*-acetylamino-2-methyl-2-butenoate ***E*-4** (36.2 mg, 0.19 mmol), methanol (6 mL), (*R*,*R*)-Me–BPE–Rh(I) (2 mg), 60 psi H_2, 20 °C, 14 h using Method 2 gave **7**, yield 98%, GC: t_R = 6.4 and 6.7 min, 49% ee. (d) (2*E*)-Ethyl 3-*N*-acetylamino-2-methyl-2-butenoate ***E*-4** (41.0 mg, 0.22 mmol), methanol (8 mL), (*R*,*R*)-Me–BPE–Rh(I) (3 mg), 15 psi H_2, 20 °C, 96 h using Method 2 gave **7**, yield 91%, GC: t_R = 6.5 and 6.7 min, 35% ee. (e) (2*E*)-Ethyl 3-*N*-acetylamino-2-methyl-2-butenoate ***E*-4** (35.0 mg, 0.19 mmol), methanol (5 mL), (*S*,*S*)-Me–DuPHOS–Rh(I) (3 mg), 60 psi H_2, 20 °C, 72 h using Method 2 gave **7**, yield 98%, GC: t_R = 6.4 and 6.7 min, 14% ee. (f) (2*E*)-Ethyl 3-*N*-acetylamino-2-methyl-2-butenoate ***E*-4** (40.0 mg, 0.22 mmol), methanol (8 mL), (*S*,*S*)-Me–DuPHOS–Rh(I) (3 mg), 15 psi H_2, 20 °C, 96 h using Method 2 gave **7**, yield 90%, GC: t_R = 6.5 and 6.7 min, 5% ee. (g) Ethyl 3-*N*-acetylamino-2-methyl-2-butenoate ***E*-4** (41.0 mg, 0.22 mmol), methanol (8 mL), (*S*,*S*)-Et–DuPHOS–Rh(I) (3 mg), 60 psi H_2, 20 °C, 72 h using Method 2 gave **7**, yield 92%, GC: t_R = 6.5 and 6.7 min, 8% ee. (h) (2*E*)-Ethyl 3-*N*-acetylamino-2-methyl-2-butenoate ***E*-4** (42.0 mg, 0.23 mmol), benzene (7 mL), (*R*,*R*)-Me–BPE–Rh(I) (3 mg), 90 psi H_2, 20 °C, 72 h using Method 2 gave **7**, yield 97%, GC: t_R = 6.5 and 6.7 min, 65% ee.

Compound **7**: Pale yellow oil; IR (neat): ν = 2982, 2361, 1723, 1652, 1540, 1456, 1374, 1266, 1194, 1033, 738, 703, 640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.15 (d, 3H, J = 6.8 Hz, H4), 1.19 (d, 3H, J = 7.2 Hz, CH_3CH), 1.28 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 1.99 (s, 3H, CH_3CO), 2.57–2.63 (m, 1H, H2), 4.13–4.19 (m, 1H, H3), 4.16 (q, 2H, J = 7.1 Hz, OCH_2CH_3), 6.32 (br d, 1H, J = 5.4 Hz, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3 (OCH_2CH_3), 15.1 (CH_3CH), 19.6 (C4), 23.6 (CH_3CO), 43.8 (C2), 47.1 (C3), 60.8 (OCH_2CH_3), 169.9 (CONH), 175.9 (C1); MS (ESI^+, H_2O/MeCN): m/z 188.2 $[(M+H)^+]$.

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