One-pot tandem enantioselective hydrogenation-hydroformylation synthesis of cyclic α-amino acids

Euneace Teoh, Eva M. Campi, W. Roy Jackson and Andrea J. Robinson*

Centre for Green Chemistry and School of Chemistry, Monash University, PO Box 23, Victoria 3800, Australia. E-mail: A.Robinson@sci.monash.edu.au; Fax: +61 03 9905 4597; Tel: +61 03 9905 4553

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Five- and six-membered cyclic amino acids can be prepared in good yield with high ee (>95%) via tandem rhodium-DuPHOS catalysed asymmetric hydrogenation followed by a rhodium-catalysed hydroformylation–cyclisation sequence in a single pot. The synthesis can be achieved using Rh-DuPHOS as the sole catalyst.

Introduction

There is a growing trend in the pharmaceutical and fine chemicals industries towards replacing classical organic synthesis with cleaner catalytic alternatives. Attention to E factor,¹ the amount of waste generated per kilo of product,² has driven chemists to reduce or eliminate the use and generation of toxic and hazardous reagents and solvents. Tandem reaction sequences employing catalytic processes therefore offer a remarkable opportunity to conduct organic synthesis in a highly efficient manner. Furthermore, reaction sequences which possess high atom economy³ and simultaneously incorporate stereochemistry into the framework of the desired target would be considered even more efficient.⁴ In this context, we have recently developed an enantioselective synthesis of cyclic α-amino acids via domino catalytic asymmetric hydrogenation-hydroformylation protocol.⁵ Cyclic amino acids are of increasing biological importance because of their relationship to naturally occurring biological molecules, e.g. the izidine alkaloids⁶ (piperidines) and kainic acid⁷ (pyrrolidines), and their use in peptidomimetics.8 The sequential transformation described herein allows the formation of a new C-C single bond and heterocycle formation with concomitant generation of a stereogenic centre. Other highly efficient domino reactions have also recently been reported and include hydroformy-lation–Knoevenagel–hydrogenation,⁹ hydroformylation–Wit-tig,¹⁰ isomerization–hydroformylation,¹¹ hydroformylation– conjugate addition¹² and isomerisation–carbonylation¹³ and isomerisation-carbonylation¹³ sequences.

In this paper, we describe an enantioselective tandem hydrogenation-hydroformylation-cyclisation sequence leading to cyclic α -amino acid derivatives.

Results and discussion

Synthesis of hydrogenation precursors

The hydrogenation precursors, the dienamide esters 1, were readily accessible by reaction of unsaturated aldehydes 2 with the phosphonate $3^{14,15}$ (Scheme 1). The Cbz-protected phosphonate 4^{15} was prepared in 81% yield and converted quantitatively into the N-acetyl-protected phosphonate 3.¹⁵ An alternative route to 3 from methyl *N*-acetyl-2-methoxyglycinate^{16,17} gave the phosphonate in a poor yield (30%). Horner–Emmons olefination¹⁸ of the phosphonate 3 was carried



out using the unsaturated aldehydes **2a–2c** (Scheme 1). The use of tetramethylguanidine (TMG) as base at low temperature in THF has been described by Burk *et al.* and the dienamide esters **1a–1c** were obtained in acceptable yields (**1a**, 55%; **1b**, 87%; **1c**, 38%) using this method.¹⁴

Asymmetric hydrogenations

The DuPHOS ligand developed by the DuPont company has been shown to give complexes with rhodium which give excellent enantioselectivities when used as catalysts in hydrogenation of prochiral substrates.¹⁹ Recently Burk *et al.* have demonstrated that high regio- and enantioselectivities can be achieved in the hydrogenation of prochiral dienamide esters.¹⁴ In this paper, the dienamide esters **1** were hydrogenated in either methanol or benzene with Rh-Et-DuPHOS using short reaction times (Scheme 2). Full conversions and high enantioselectivity (ee) were achieved in methanol (>80% ee) and benzene (>95% ee) (Table 1). As the substrates were more soluble



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Table 1 Rh-catalysed asymmetric hydrogenation of dienamide esters $\mathbf{1}^{a}$

Entry	Substrate	R	n	Pressure/ psi	Time/ h	Product	Ratio ^b 5:6	Yield (%) ^c	$\frac{\%}{ee^d}$
1	1a	Me	0	90	2	5a	94:6	99	95
2	1a	Me	0	90	2	5a	95:5	98	95 ^e
3	1b	Н	0	30	3	5b	95:5	88	95
4	1b	Н	0	30	3	5b	95:5	90	76 ^f
5	1b	Н	0	30	3	5b	95:5	90	95 ^e
6	1c	Н	2	30	2	5c	92:8	90	98

^{*a*} All reactions were performed in benzene using Rh-(*R*,*R*)-Et-DuPHOS with substrate:catalyst ratio = 100:1 at ambient temperature, 100% conversion was observed in all cases. For specific conditions, refer to experimental. ^{*b*} % Over-reduction was estimated by ¹H NMR. ^{*c*} Isolated yield of **5**+**6** after passage through a short plug of silica. ^{*d*} % ee of **5** was assessed by chiral capillary GC column (CP-Chirasil Val). ^{*e*} Reaction using Rh-(*S*,*S*)-Et-DuPHOS giving (*S*)-**5**. ^{*f*} Reaction carried out in methanol.

in benzene and the % ee was found to be higher, subsequent reactions were carried out in benzene. An increase in pressure, reaction duration and catalyst loading increased the amount of over-reduction.¹⁴ For unsubstituted dienamide esters **1b** and **1c** (entries 3 to 6), a low pressure (30 psi of H₂) and short reaction time (2–3 h) were used to give < 8% of the over-reduced by-product **6** with 100% conversion of starting material **1**. In contrast for the substituted substrate **1a** (entries 1 and 2), higher pressure (90 psi of H₂) was needed for the hydrogenation to go to completion in 2 h. In all cases, the products were isolated in high yields. Enantiomeric excess was assessed by chiral capillary GC.

Hydroformylation

Preparation of pyrrolidine and piperidine derivatives. Heterocyclic compounds can be obtained in good yields by a hydroformylation-cyclisation reaction sequence from unsaturated amines and amides.^{20,21} Ojima *et al.* have applied this methodology to the preparation of pipecolic acid derivatives by hydroformylation of enamides related to 1b.22 High regioselectivity was obtained when the bulky phosphite BIPHEPHOS²³ was used as a ligand. The methodology has now been applied to reactions of the chiral enamides 5, leading predominantly to the cyclic amido esters 9 and 10 presumably via the aldehydes 7 and 8 as shown in Scheme 3. The reactions were carried out using Rh/PPh3 or Rh/BIPHEPHOS under 400 psi of CO/ H_2 (1:1) and gave the piperidine 9 and pyrrolidine 10 derivatives. The 5- and 6-membered ring compounds were readily separated by chromatography and chiral HPLC showed that the enantiomeric excess (ee) of these compounds was preserved (Table 2). Hydroformylation of enamide 5a using the PPh₃

388 New J. Chem., 2003, **27**, 387–394

Table 2 Rh-catalysed hydroformylation of hydrogenated enamides **5a**; $\mathbf{R} = \mathbf{Me}$ and **5b**; $\mathbf{R} = \mathbf{H}^{a}$

Entry	R	Catalyst system	CO/ H ₂ /psi	<i>T</i> /°C	Time/ h	Product ratio 9:10	Yield $(\%)^b$	% ee ^c 9/10
7	Me	А	400	80	20	67:33	45	91/98
8	Me	В	400	80	20	100:0	37^d	_
9	Me	В	400	100	72	91:9	81	97/98
10	Me	А	400	80	20	80:20	47^e	_
11	Н	А	400	80	72	50:50	73	—/87
12	Н	В	400	80	20	63:37	66	88/—
13	Н	В	100	80	20	71:29	54 ^f	/87
14	Н	В	80	80	20	78:22	g	
15	Н	В	80	80	72	66:34	75	99/99

^{*a*} Reaction conditions: substrate:[Rh(OAc)_2]_2:PPh₃ or BIPHEPHOS ratio = 100:1:2 in benzene (5–10 mL), A = Rh-PPh₃ and B = Rh-BIPHE-PHOS. For specific conditions, refer to experimental. ^{*b*} Isolated yield of cyclic products **9** and **10** after chromatography. ^{*c*} % ee was assessed by chiral HPLC column (DAICEL Chiraclel[®] OD); — Signifies that enantiomeric excess (ce) was not assessed. ^{*d*} Aldehydes **7a** and **8a** (*ca.* 1:1) also obtained. ^{*e*} Initial isolation of amidals **11** and **12**. ^{*f*} Crude product contained *ca.* 20% isomerised alkenamide **13**. ^{*g*} Crude product contained *ca.* 50% isomerised alkenamide **13**.

ligand gave **9a** and **10a** in a 2:1 ratio (entry 7), whilst under the same conditions, use of the BIPHEPHOS ligand led to incomplete cyclisation and isolation of aldehydes **7a** and **8a** (entry 8). Reaction using BIPHEPHOS at the same pressure but with increased temperature and reaction time gave complete conversion with a higher ratio of piperidine **9a** to pyrrolidine **10a** (9:1 ratio) (entry 9) consistent with the bulky ligand directing the initial hydroformylation to the less hindered carbon of the alkene. In one reaction using PPh₃ as ligand, the initial product contained the amidals **11** and **12** which dehydrated on standing in CDCl₃ to give the enamides **9a** and **10a** (entry 10). Similar amidals have been isolated by Ojima and coworkers.^{20,22}

Hydroformylation of 5b, containing a terminal alkene, surprisingly gave a lower than expected piperidine 9b:pyrrolidine 10b ratio in all cases. Reaction of 5b using the PPh₃ ligand gave a 1:1 ratio of the cyclic amino acid derivatives 9b and 10b (entry 11), in contrast to the ca. 2:1 ratio obtained with 5a. Reaction using BIPHEPHOS gave 9b and 10b in a ratio of 2:1, again lower than the ratio of >9:1 usually obtained for hydroformylation of terminal alkenes with this ligand²³ (entry 12). A reaction using 100 psi CO/H_2 and the BIPHEPHOS ligand led to formation of the isomerised alkenamide 13 in ca. 20% yield (entry 13). This isomer would preferentially be hydroformylated and cyclised to give pyrrolidine 10b, which explains the unexpected higher ratio of pyrrolidine 10b in the reactions. A reaction at even lower pressure (80 psi) gave ca. 50% of the isomerised alkenamide 13 (entry 14). Extending the reaction time under these conditions gave the cyclic products 9b and 10b in 75% yield (entry 15).

This result is very unexpected in that, although alkene isomerisation by related rhodium compounds is well established, the terminal alkene normally hydroformylates faster than internal alkenes. Thus, such a phenomenon is consistent with the recently reported high yields of straight chain aldehydes from hydroformylation of internal alkenes using a Rh-NAPHOS catalyst.²⁴ Similarly, a tandem isomerisation–carbonylation sequence gave linear esters from a Pd-catalysed carbonylation of internal alkenes.¹³ One possible explanation for this result is that chelation of rhodium to the amido carbonyl leads to preferential hydroformylation of the internal double bond as is the case for the preceding hydrogenation reaction.^{19,25}

One-pot tandem reactions. The possibility of carrying out the hydrogenation-hydroformylation sequence in a single pot was examined (Scheme 4). Hydrogenation of the dienamides **1a** and **1b** was carried out in a vessel containing both the Rh-DuPHOS and either Rh-BIPHEPHOS or Rh-PPh₃ catalysts.





After the low pressure hydrogenation was complete, the gas was vented and replaced by a 1:1 CO/H₂ gas mixture and the temperature raised to 80 °C. Good to very good yields of the heterocycles 9 and 10 were obtained (Table 3, entries 16 and 17). Excellent enantioselectivity (>95% ee) of 9 and 10 was maintained, showing that there was no significant competition by Rh-BIPHEPHOS or Rh-PPh₃ in the hydrogenation step catalysed by Rh-DuPHOS. Reaction of the terminal alkene 1b gave some isomerised alkene 13 (25%) in addition to the heterocycles 9b and 10b (Table 3, entry 17).

The possibility of using Rh-DuPHOS as a catalyst for both reactions was investigated. This catalyst has not been used previously for hydroformylation reactions. Reactions of dienamide substrates 1a and 1b using Rh-Et-DuPHOS, initially under hydrogenation conditions and then under hydroformylation conditions, gave the expected cyclic products 9 and 10 in reasonable yields (Table 3). Again, the enantiomeric excess (ee) was found to be excellent (>98%). Comparison of the results reported in entries 9 (Table 2) and 19 (Table 3) suggests that Rh-DuPHOS appears to be a slightly less efficient catalyst than Rh-BIPHEPHOS as it needed more forcing conditions to give complete conversion of dienamide 1a to cyclic products 9a and 10a. Comparison of entries 7 (Table 2) and 18/19 (Table 3) shows that Rh-DuPHOS is also less efficient than the Rh-PPh₂ system. A similar scenario was observed in reaction of dienamide 1b, as it too required higher pressure to achieve 100% completion and 91% isolated yield of 9b and 10b (compare entries 15 (Table 2) and 20/21 (Table 3)).

Attempted preparation of 7- and 8-membered cyclic amino acid derivatives. Attempts were made to extend the method to the preparation of larger ring cyclic amido esters from a longer chain hydrogenation precursor (Scheme 5) and the results are summarised in Table 4. The enamide ester 5c was

Table 3 One-pot tandem reaction of dienamide esters 1a; R = Me and 1b; $R = H^a$

Entry	R	Catalyst system	CO/ H ₂ /psi	<i>T/</i> °C	Time/ h	Product ratio 9:10	Yield $(\%)^b$	% ee ^c 9/10
16	Me	A+C	400	80	20	56:44	81	95/99
17	Н	B + C	80	80	72	67:33	60^d	95/95
18	Me	С	400	80	20	83:17	35^e	99/99
19	Me	С	800	150	72	100:0	58	96/—
20	Н	С	80	80	72	74:26	f	
21	Н	С	400	80	72	54:46	91	95/99

^{*a*} Reaction conditions: substrate:Rh-Et-DuPHOS:[Rh(OAc)₂]₂:PPh₃ or BIPHE-PHOS ratio = 100:1:1:2 in benzene (5–10 mL) with H₂ (90 psi, 2 h for **1a** and 30 psi, 3 h for **1b**) at ambient temperature followed by CO/H₂ (1:1 ratio), A = Rh-PPh₃, B = Rh-BIPHEPHOS and C = Rh-Et-DuPHOS. ^{*b*} Isolated yield of cyclic products **9** and **10** after chromatography. ^{*c*} % ee was assessed by chiral HPLC column (DAICEL Chiralcel[®] OD); — Signifies that enantioselectivity was not assessed. ^{*d*} Isomerised alkene **13** also isolated (25% yield). ^{*e*} Aldehydes **7a** and **8a** also obtained (*ca.* 15%). ^{*f*} Crude product contained *ca.* 40% isomerised alkenamide **13**.



hydroformylated using the Rh-PPh₃ and Rh-BIPHEPHOS systems and gave the aldehydes **14** and **15** (entries 22 and 23). No cyclic material was observed.

A one-pot tandem reaction was carried out using a higher pressure and temperature for a longer period of time with the mixed Rh-DuPHOS and Rh-BIPHEPHOS catalysts (Table 4, entry 24). The major product was the saturated compound **6c**. Chromatography gave a mixture of the two heterocycles **17** and **18** in *ca*. 1:1 ratio and *ca*. 24% yield. No 8-membered ring compound **16** was detected. Formation of **18** means that some of the aldehyde **19** has been generated *via* initial alkene isomerisation.

A one-pot reaction using only Rh-DuPHOS as catalyst under the same conditions again gave predominantly the saturated compound **6c** (Table 4, entry 25). Chromatography led to the isolation of the 6-ring compound **18** in 12% yield. The difficulty associated with the formation of 7- and 8-membered rings accounts for the low yields of heterocycles but the formation of large amounts of hydrogenated rather than hydroformylated material is hard to understand.

Preparation of a cyclic α -amino acid. The piperidine 9b prepared using (R,R)-Et-DuPHOS-Rh was converted into the pipecolic acid hydrochloride 21 (Scheme 6)and its optical

Table 4 Attempted synthesis of 7- and 8-membered cyclic amino $acids^{a}$

Entry	Substrate	Catalyst system	CO/H ₂ / psi	T/ °C	Time/ h	Product ratio ^b 17:18	Yield (%) ^c
22	5c	А	400	80	20	d	_
23	5c	В	400	80	20	е	
24	1c	B + C	800	150	72	50:50 ^f	12
25	1c	С	800	150	72	$0:100^{g}$	24

^{*a*} Reaction conditions: substrate:Rh-Et-DuPHOS:[Rh(OAc)₂]₂:PPh₃ or BIPHE-PHOS ratio = 100:1:1:2 in benzene (5–10 mL) with 30 psi of H₂ for 2 h at ambient temperature followed by CO/H₂ (1:1 ratio), A = Rh-PPh₃, B = Rh-BIPHEPHOS and C = Rh-Et-DuPHOS. ^{*b*} — Signifies that no cyclic products were observed. ^{*c*} Isolated yield of cyclic products **17** and **18** after chromatography. ^{*d*} Aldehydes **14** and **15** were obtained in 1:1 ratio (63% yield). ^{*e*} Aldehydes **14** and **15** present in 1:1 ratio; not isolated. ^{*f*} Crude product contained *ca*. 74% over-reduced by-product **6c**. ^{*g*} Crude product contained *ca*. 67% over-reduced by-product **6c**.



rotation, $[\alpha]_D + 10^\circ$ was almost identical to a literature $[\alpha]_D + 10.8^\circ$ for the (*R*)-enantiomer.²⁶ Thus the initial enantioselective hydrogenation using Rh-(*R*,*R*)-Et-DuPHOS was highly selective for the (*R*)-configuration of the product in agreement with previous findings.^{19,27}

Conclusion

High yields of 5- and 6-membered ring α -amino acid derivatives, *viz*. the piperidines **9** and pyrrolidines **10**, can be obtained with high ee using one or two catalysts in a one-pot reaction. The reaction involves a tandem hydrogenation, hydroformylation, cyclisation sequence. It has been demonstrated that Rh-DuPHOS can act as an efficient catalyst for hydroformylation as well as hydrogenation reactions.

Reactions of glycine derivatives **1a** and **1b**, substituted with 1,3-dienes, gave surprisingly high ratios of products arising from branched as opposed to linear aldehydes. Similarly, reactions of the homologous 1,5-diene derivative **1c** gave the 6- and 7-membered ring heterocycles **18** and **17**, suggesting that isomerisation competes with hydroformylation and that formation of internal aldehydes is favoured, possibly because of intramolecular chelation of the rhodium catalyst to the oxygen of the acetamido carbonyl group.

Experimental

¹H NMR and ¹³C NMR spectra were recorded at 300 MHz and 75 MHz respectively with a Varian Mercury 300 Q Spectrometer in CDCl₃ and referenced to Me₄Si unless otherwise stated. ³¹P NMR spectra were recorded at 121.5 MHz on a Bruker AM-300 spectrometer in deuterated solvents with 85% phosphoric acid (H₃PO₄) as the external standard. EI mass spectra were recorded on a Hewlett Packard Trio-1 spectrometer operating at 200 °C/70 eV. ESI mass spectra were recorded on a Micromass Platform spectrometer. HRMS were recorded on a Bruker BioApex 47e Fourier transform mass spectrometer.

Analytical gas chromatography (GC) was carried out using a Chrompack CP-Chirasil Val chiral column (column: 0.25 mm × 50 m, 50 CP2/XE-60-S-VAL-S-A-PEA) using helium as the carrier gas and follows the temperature program: initial column temperature was 100 °C for 1 min, then heated to 280 °C for 9 min at 5 °C min⁻¹. High performance liquid chromatography (HPLC) was carried out on a Varian LC Model 5000 instrument with a Varian UV-50 detector and using a DAICEL Chiralcel® OD column. The solvent system used was 10% isopropanol:90% hexane with a flow rate of 1.0 mL min^{-1} . A solution (10 µL) of the purified compound in HPLC grade isopropanol was used for injection. Optical rotations $[\alpha]_D^{20}$ were measured using a Perkin Elmer Model 141 Polarimeter. Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. Microanalysis were carried out by Chemical and Microanalytical Services Pty. Ltd., Melbourne (CMAS).

Materials

[(COD)Rh-((2R,5R)-Et-DuPHOS)]OTf and [(COD)Rh-((2S,5S)-Et-DuPHOS)]OTf were used as supplied from Strem

Chemicals. $[Rh(OAc)_2]_2$ and BIPHEPHOS²² were prepared by Eva M. Campi. PPh₃ was obtained from Aldrich. H₂ and 1:1 molar mixture of CO/H₂ were obtained from BOC gases.

Synthesis of hydrogenation precursors

Methyl 2-benzyloxycarbonylamino-2-(dimethoxyphosphinyl)acetate 4. The Cbz-protected phosphonate 4 was prepared as described by Schmidt¹⁵ from methyl *N*-benzyloxycarbonyl-2methoxyglycinate^{16,17} (23.0 g, 90.81 mmol) as a white solid, (24.33 g, 81%); mp 77–78 °C (lit.¹⁵ 80 °C). ¹H NMR: δ [minor rotamer in brackets] 3.77–3.83 (m, 9H, COOCH₃, $2 \times$ CH₃OP), 4.93 (dd, 1H, J = 22.4, 9.3 Hz, [5.12, bd, $J \sim$ \approx 8.2 Hz], H2), 5.13 (d, 1H, J = 12.2 Hz) and 5.15 (d, 1H, J = 12.1 Hz, CH₂O), 5.77 (bd, 1H, $J \sim$ 8.2 Hz, [6.21, bs], NH), 7.32–7.40 (m, 5H, ArH). ¹³C NMR: δ [minor rotamer in brackets] 52.4 (d, J = 148.0 Hz, [73.9, s], C2), 53.7 [53.5] (COOCH₃), 54.4 (d, J = 6.9 Hz, CH₃OP), 54.5 (d, J = 6.6Hz, CH₃OP), 67.9 [67.7] (CH₂O), 128.4, 128.5, 128.8 (ArCH), 136.0 (C1'), 155.8 [155.9] (CONH), 167.3 [170.0] (C1). ³¹P NMR: δ 19.62 (s). MS (ESI⁺, MeOH): m/z 354.1 (M + Na)⁺.

Methyl 2-acetylamino-2-(dimethoxyphosphinyl)acetate 3. The *N*-acetyl phosphonate 3 was prepared as described by Schmidt *et al.*¹⁵ from the phosphonate 4 (10.0 g, 30.18 mmol) as a white solid (8.06 g, 100%); mp 90–92 °C (lit.¹⁵ 88–89 °C). ¹H NMR: δ 2.06 (s, 3H, COCH₃), 3.79–3.81 (m, 9H, COOCH₃, $2 \times$ CH₃OP), 5.24 (dd, 1H, J = 22.3, 8.5 Hz, H2), 6.74 (d, 1H, J = 8.6 Hz, NH). ¹³C NMR: δ 23.3 (COCH₃), 49.3 (d, J = 147.2 Hz, C2), 53.7 (COOCH₃), 54.3 (d, J = 6.6 Hz, CH₃OP), 54.6 (d, J = 6.3 Hz, CH₃OP), 167.3 (d, J = 2.0 Hz, C1), 169.7 (d, J = 5.7 Hz, CONH). MS (ESI⁺, MeOH): m/z 262.0 (M + Na)⁺.

An alternative route to the phosphonate **3** involved reaction of methyl *N*-acetyl-2-methoxyglycinate^{16,17} (1.01 g, 6.27 mmol) with phosphorus(III) chloride (0.55 mL, 6.27 mmol) and trimethyl phosphite (0.74 mL, 6.27 mmol) at 70 °C as described for the preparation of the Cbz-protected phosphonate **4**¹⁵ to give **3** as a white solid (0.43 g, 30%).

4-Pentenal 2c. Following the method described by Swern *et al.*,^{28,29} reaction of 4-penten-1-ol (1.0 mL, 9.70 mmol) with dimethyl sulfoxide (1.52 mL, 21.34 mmol), oxalyl chloride (0.93 mL, 10.67 mmol) and triethylamine (6.76 mL, 48.50 mmol) gave an oil (1.30 g). The ¹H and ¹³C NMR spectra indicated that the crude oil was a mixture of 4-pentenal **2c** and starting material (δ 3.62, t, CH₂) in an ratio of ~1:0.2. (approximate yield for **2c** was 83%). The crude product was used in the preparation of (2*Z*)-methyl 2-acetamidohepta-2,6-dienoate **1c**. ¹H NMR: δ 2.13 (q, 2H, *J* = 7.0 Hz, H3), 2.39 (td, 2H, *J* = 7.0, 1.4 Hz, H2), 4.94–5.10 (m, 2H, H5), 5.82 (ddt, 1H, *J* = 17.1, 10.2, 6.3 Hz, H4), 9.78 (t, 1H, *J* = 1.5 Hz, H1). ¹³C NMR: δ 26.2 (C3), 42.8 (C2), 115.5 (C5), 136.4 (C4), 201.7 (C1). The spectral data were consistent with literature data.³⁰

(2Z,4E)-Methyl 2-acetamidohexa-2,4-dienoate 1a. Tetramethylguanidine (0.61 mL, 4.89 mmol) was added to a solution of methyl 2-acetylamino-2-(dimethoxyphosphinyl) acetate 3 (0.88 g, 3.68 mmol) in distilled THF (15 mL) at -78 °C following the method described by Burk.¹⁴ After 15 min, crotonaldehyde 2a (0.40 mL, 4.42 mmol) was added and the mixture was stirred for 2 h at -78 °C. The mixture was warmed to 25 °C using a warm water bath and stirred at this temperature for a further 2 h. The mixture was diluted with CH₂Cl₂ (20 mL), washed with 1 M HCl (2 × 10 mL), 1 M CuSO₄(2 × 10 mL), saturated NaHCO₃ (2 × 10 mL) and 1 M NaCl (10 mL). The organic layer was dried with MgSO₄ and concentrated under reduced pressure to give an oil (0.90 g). Purification by flash chromatography on silica gel using ethyl acetate and light petroleum (2:1) gave the dienoate **1a** as a white solid (0.37 g, 55%), (R_f 0.21), mp 88–90 °C (lit.¹⁴ 89– 90.1 °C). ¹H NMR: δ 1.88 (d, 3H, J = 5.2 Hz, H6), 2.16 (s, 3H, COCH₃), 3.17 (s, 3H, COOCH₃), 6.16–6.20 (m, 2H, H4, H5), 6.90 (bs, 1H, NH), 7.08 (d, 1H, J = 10.1 Hz, H3). ¹³C NMR: δ 19.3 (C6), 23.6 (COCH₃), 52.6 (COOCH₃), 121.6 (C2), 126.9, 134.5, 139.7 (C3, C4, C5), 165.7, 169.2 (C1, CONH).MS (ESI⁺, MeOH): m/z 206.0 (M + Na)⁺.

(2Z)-Methyl 2-acetamidopenta-2,4-dienoate 1b. Using the method described above, tetramethylguanidine (1.90 mL, 14.90 mmol) and hydroquinone (5 mg) were added to a solution of the phosphonate 3 (3.0 g, 11.23 mmol) in distilled THF (35 mL) at -78 °C. After 15 min, acrolein 2b (0.90 mL, 13.47 mmol) was added, the mixture stirred at $-78 \,^{\circ}\text{C}$ for 2 h then at 25 °C for 2 h and worked up to give an oil (2.81 g). Purification by flash chromatography on silica gel using ethyl acetate and light petroleum (1:1) gave the (2Z)-dienoate **1b** as a white solid (1.65 g, 87%), (R_f 0.2); mp 61–63 °C. IR (KBr): 3277, 3011, 2955, 1733, 1655, 1594, 1518, 1438, 1113, 1016, 994, 950, 768 cm⁻¹. ¹H NMR: δ 2.14 (s, 3H, COCH₃), 3.79 (s, 3H, COOCH₃), 5.47 (d, 1H, J = 10.1 Hz, H5_(E)), 5.59 (d, 1H, J = 16.9 Hz, H5_(Z)), 6.39–6.52 (m, 1H, H4), 7.03 (d, 1H, J = 11.3 Hz, H3), 7.12 (bs, 1H, NH). ¹³C NMR: δ 23.8 (COCH₃), 52.8 (COOCH₃), 132.1, 132.9 (C3, C4), 123.7 (C2), 125.2 (C5), 165.6, 168.8 (C1, CONH). Calc. for C₈H₁₁NO₃: C, 56.78; H, 6.54; N, 8.28. Found: C, 56.66; H, 6.67; N, 8.29%.

(2Z)-Methyl 2-acetamidohepta-2,6-dienoate 1c. Reaction of tetramethylguanidine (0.31 mL, 3.95 mmol) and the phosphonate 3 (0.71 g, 2.97 mmol) in distilled THF (10 mL) with 4-pentenal 2c (0.69 mL, 3.57 mmol) as described above gave an oil (0.47 g). Purification by flash chromatography on silica gel using ethyl acetate and light petroleum (1:1) gave the (2Z)-dienoate 1c as a white solid (0.22 g, 38%), (R_f 0.24); mp 44–45 °C (lit.¹⁵ 44 °C). ¹H NMR: δ 2.10 (s, 3H, COCH₃), 2.16–2.29 (m, 4H, H4, H5), 3.75 (s, 3H, COOCH₃), 4.97–5.08 (m, 2H, H7), 5.79 (ddt, 1H, J = 17.1, 10.4, 6.4 Hz, H6), 6.64 (t, 1H, J = 6.6 Hz, H3), 7.90 (bs, 1H, NH). ¹³C NMR: δ 23.2 (COCH₃), 28.0 (C4), 32.3 (C5), 52.3 (COOCH₃), 115.5 (C7), 125.9 (C2), 137.0 (C3), 138.0 (C6), 165.0, 169.2 (C1, CONH). MS (ESI⁺, MeOH): m/z 220.1 (M + Na)⁺.

Asymmetric hydrogenations

In a dry box, the substrate, catalyst (substrate:catalyst = 100:1) and deoxygenated methanol or benzene were added into a Fischer–Porter tube. Three vacuum/nitrogen cycles were used to purge the gas line of any oxygen, followed by three vacuum/nitrogen cycles and three vacuum/hydrogen cycles of the vessel before the vessel was pressurized to the stated pressure with hydrogen. The vessel was left stirring at ambient temperature for the reported period of time. For liquid substrates, a freeze–pump–thaw cycle was applied, the solution was transferred into a dry box and loaded into a Fischer–Porter tube.

(2*R*,4*E*)-Methyl 2-acetamidohex-4-enoate 5a. (2*Z*,4*E*)-Methyl 2-acetamidohexa-2,4-dienoate 1a (0.42 g, 2.18 mmol) and [(COD)Rh-(*R*,*R*)-Et-DuPHOS]OTf were dissolved in benzene (10 mL). The vessel was charged with hydrogen (90 psi) and the mixture stirred for 2 h. The hydrogen was vented and the mixture was concentrated to give an oil (0.42 g). Purification by passing through a short silica plug with ethyl acetate gave an oil (0.40 g, 99%). The ¹H NMR spectrum of the oil indicated the (2*R*,4*E*)-hex-4-enoate 5a and the fully saturated compound, (2*R*,4*E*)-methyl 2-acetamidohexanoate 6a [δ 0.89 (m, CH₃), 1.22–1.39 (m, CH₂)] in a 94:6 ratio respectively. IR (neat) 3284, 2954, 1747, 1658, 1547, 1437, 1375, 1217,

1142, 968 cm⁻¹. ¹H NMR: δ 1.67 (ddt, 3H, J = 6.4, 1.7, 1.1 Hz, H6), 2.03 (s, 3H, COCH₃), 2.43–2.51 (m, 2H, H3), 3.75 (s, 3H, COOCH₃), 4.63 (dt, 1H, J = 7.8, 5.6 Hz, H2), 5.28 (m, 1H, H5), 5.55 (dqt, 1H, J = 15.1, 6.4, 1.2 Hz, H4), 5.98 (bs, 1H, NH). ¹³C NMR: δ 18.3 (C6), 23.4 (COCH₃), 35.6 (C3), 52.3, 52.6 (C2, COOCH₃), 124.6, 130.1 (C4, C5), 169.8, 172.6 (C1, CONH). MS (ESI⁺, MeOH): m/z 207.9 (M + Na)⁺. [α]_D²² –55° (c 1.18, CHCl₃) containing 6% of **6a** (lit.¹⁴ [α]_D²⁰ –57.2° (c 1.18, CHCl₃) containing <2% of **6a**).

(2R)-Methyl 2-acetamidopent-4-enoate 5b. Hydrogenation of (2Z)-methyl 2-acetamidopenta-2,4-dienoate 1b (40 mg, 0.24 mmol) in benzene was carried out at 30 psi for 3 h using Rh-(R,R)-Et-DuPHOS. Purification by passing through a short plug of silica with ethyl acetate gave an oil (36 mg, 88%). The ¹H NMR spectrum indicated the (2R)-pent-4-enoate 5b and the fully saturated compound, (2R)-methyl 2-acetamidopentanoate **6b** [δ 0.93 (t, J = 7.3 Hz, CH₃), 1.25–1.44 (m, CH₂)] in a 95:5 ratio respectively. A solution of the oil in dichloromethane (2 mL) was injected into the GC chiral column to give two peaks: (R), $t_1 = 18.2$ min; (S), $t_2 = 18.6$ min; ee 95% (R). IR (neat): 3278, 1744, 1657, 1546, 1438, 1375, 1151 cm⁻¹. ¹H NMR: δ 2.00 (s, 3H, COCH₃), 2.42– 2.61 (m, 2H, H3), 3.72 (s, 3H, COOCH₃), 4.66 (m, 1H, H2), 5.09 (d, 1H, J = 16.2 Hz, H5_(Z)), 5.10 (d, 1H, J = 11.1Hz, $H5_{(E)}$), 5.65 (m, 1H, H4), 6.14 (bs, 1H, NH). ¹³C NMR: δ 23.4 (COCH₃), 51.8, 52.5 (C2, COOCH₃), 119.2 (C5), 132.2 (C4), 169.7, 172.2 (C1, CONH). HRMS (ESI+, MeOH): calc. for $(C_8H_{13}NO_3 + Na)^+ m/z$ 194.0793, found 194.0785 $(M + Na)^+$. $[\alpha]_D^{22} - 43^\circ$ (c 0.047, CH₃Cl) containing 5% of 6b.

(2R)-Methyl 2-acetamidohept-6-enoate 5c. Hydrogenation of (2Z)-methyl 2-acetamidohepta-2,6-dienoate 1c (40 mg, 0.20 mmol) in benzene was carried out at 30 psi for 2 h using Rh-(R,R)-Et-DuPHOS. Purification by passing through a short plug of silica with ethyl acetate gave an oil (36 mg, 90%). The ¹H NMR spectrum indicated the (2R)-hept-6-enoate 5c and the fully saturated compound, (2R)-methyl 2-acetamidoheptanoate **6c** [(δ 0.88 (t, J = 6.6 Hz, CH₃)] in a 92:8 ratio respectively. A solution of the oil in dichloromethane (2 mL) was injected into the GC chiral column to give two peaks: (R), $t_1 = 25.9$ min; (S), $t_2 = 26.1$ min; ee 98% (R). IR (neat): 3286, 2954, 1745, 1658, 1547, 1436, 1374, 1264, 1210 cm⁻¹. ¹H NMR: δ 1.26–1.53 (m, 2H, H4), 1.58–1.91 (m, 2H, H3), 2.03 (s, 3H, COCH₃), 2.06-2.10 (m, 2H, H5), 3.75 (s, 3H, COOCH₃), 4.61 (td, 1H, J = 7.7, 5.5 Hz, H2), 4.95–5.05 (m, 2H, H7), 5.75 (ddt, 1H, J = 17.0, 10.4, 6.5 Hz, H6), 6.30 (bs, 1H, NH). ¹³C NMR: δ 23.5 (COCH₃), 24.8 (C4), 32.2 (C3), 33.5 (C5), 52.4, 52.7 (C2, COOCH₃), 115.3 (C7), 138.0 (C6), 170.1, 173.3 (C1, CONH). HRMS (EI, MeOH): calc. for $(C_{10}H_{17}NO_3-COCH_3)$ m/z 156.1024, found 156.1024 (M–COCH₃). $[\alpha]_D^{22}$ –60° (*c* 0.15, CH₃Cl) containing 8% of 6c.

Hydroformylations

Reactions with CO/H_2 were carried out in a 100 mL Parr stainless steel autoclave fitted with a glass liner and magnetic stirrer bead.^{21,31} After the reagents and substrate had been added under nitrogen into the autoclave, the vessel was flushed three times with 100 psi of CO/H_2 (1:1 molar ratio) and then pressurized to the stated pressure of the same gases. The autoclave was inserted to the heating block where its temperature was controlled by a thermocouple and the reaction was stirred with a magnetic stirrer under the heating block. The vessel was left stirring at the reported temperature for the reported period of time. At the end of the reaction, the vessel was left to cool to ambient temperature. The gases were released slowly and the contents were treated and analyzed as reported.

Reaction of (2R,4E)-methyl 2-acetamidohex-4-enoate 5a. (2*R*)-Methyl N-acetyl-5-methyl-5,6-didehydropipecolate **9**a and (2R)-methyl N-acetyl-4-ethyl-4,5-didehydroprolinate 10a. (2R,4E)-Methyl 2-acetamidohex-4-enoate 5a (40 mg, 0.22 mmol), rhodium(II) acetate dimer (1.0 mg, 2.2 µmol) and BIPHEPHOS (3.5 mg, 4.4 µmol) were dissolved in deoxygenated benzene (5 mL). The autoclave was pressurized to 400 psi of CO/H₂ (1:1 molar ratio) and heated to 100 °C. After 72 h, the autoclave was cooled to ambient temperature and the solvent was removed under reduced pressure to give an brown oil (50 mg). The ¹H and ¹³C NMR spectra of the crude oil showed the pipecolate 9a and the prolinate 10a in a 91:9 ratio respectively. The compounds were separated by chromatography on silica gel using ethyl acetate and light petroleum (3:1 ratio).

(2*R*)-Methyl *N*-acetyl-5-methyl-5,6-didehydropipecolate **9a** was isolated as clear oil (30 mg, 70%), ($R_{\rm f}$ 0.51). HPLC: (*S*), $t_1 = 7.9$ min; (*R*), $t_2 = 10.5$ min; ee 97% (*R*). IR (neat): 1744, 1654, 1404, 1205, 1174 cm⁻¹. ¹H NMR: δ [minor rotamer in brackets] 1.70 (s, 3H, [1.74, s], CH₃C5), 1.80–2.00 (m, 3H, H3, H4a), 2.22 (s, 3H, [2.11, s], COCH₃), 2.37 (m, 1H, H4b), 3.71 (s, 3H, [3.76, s], COOCH₃), 5.23 (m, 1H, [4.60, bs], H2), 6.40 (s, 1H, [7.04, s], H6). ¹³C NMR: δ [minor rotamer in brackets] 21.4 [21.2] (CH₃C5), 21.75 [21.85] (COCH₃), 23.7 [24.2] (C3), 24.7 [24.3] (C4), 51.3 [53.1] (C2), 52.7 [55.4] (COOCH₃), 116.1 [116.7] (C5), 120.1 [118.4] (C6), 168.2, 171.3 (C1, CONH). Calc. for C₁₀H₁₄NO₃: C, 60.88; H, 7.67; N, 7.10. Found: C, 60.74; H, 7.69; N, 6.96%. [α]_D²⁰ +138° (*c* 0.034, CH₃Cl).

(2*R*)-Methyl *N*-acetyl-4-ethyl-4,5-didehydroprolinate (**10a**) was obtained as clear oil (5 mg, 11%), (R_f 0.34). HPLC: (S), t₁ = 11.0 min; (R), t₂ = 18.7 min; ee 98% (*R*). IR (neat): 2858, 1750, 1647, 1438, 1208 cm⁻¹. ¹H NMR: δ 1.08 (t, 3H, *J* = 7.5 Hz, CH₃CH₂), 2.03–213 (m, 2H, CH₃CH₂), 2.15 (s, 3H, COCH₃), 2.52 (dd, 1H, *J* = 16.8, 5.1 Hz, H3a), 2.96 (dd, 1H, *J* = 16.7, 11.7 Hz, H3b), 3.76 (s, 3H, COOCH₃), 4.82 (dd, 1H, *J* = 11.7, 5.2 Hz, H2), 6.19–6.21 (m, 1H, H5). ¹³C NMR: δ 12.5 (CH₃CH₂), 21.8 (C3), 21.9 (COCH₃), 36.7 (CH₃CH₂), 52.7, 58.7 (C2, COOCH₃), 122.9 (C5), 126.4 (C4), 166.0, 171.9 (C1, CONH). HRMS (EI, MeOH): calc. for C₁₀H₁₅NO₃ *m/z* 197.1052, found 197.1046 (M). $[\alpha]_D^{20}$ +114° (*c* 0.028, CH₃CI).

A similar reaction using BIPHEPHOS at 80 °C, 400 psi gave a mixture of the aldehydes **7a** and **8a** (ratio *ca.* 1:1) and the pipecolate **9a**. ¹H NMR: δ for **7a**, 9.61 (d, J = 1.5 Hz, CHO); for **8a**, 9.76 (d, J = 1.5 Hz, CHO). The pipecolate **9a** was isolated in 37% yield.

A reaction of the hex-4-enoate **5a** (50 mg, 0.27 mmol), rhodium(II) acetate dimer (1.2 mg, 2.7 µmol) and triphenylphosphine (1.4 mg, 5.4 µmol) at 80 °C with 400 psi of CO/H₂ for 20 h gave a brown oil (64 mg). The ¹H and ¹³C NMR spectra of the crude oil showed (2*R*)-methyl *N*-acetyl-5methyl-6-hydroxypipecolate **11** and (2*R*)-methyl *N*-acetyl-4ethyl-5-hydroxyprolinate **12** in 4:1 ratio. The compounds were separated using column chromatography (ethyl acetate).

(2*R*)-methyl *N*-acetyl-5-methyl-6-hydroxypipecolate **11**: ¹H NMR. δ 1.07 (d, 3H, J = 9.0 Hz, CH₃–C5), 1.31–1.79 (m, 5H, H3, 4 5), 2.22 (s, 3H, COCH₃), 3.71 (s, 3H, COOCH₃), 4.39 (t, 1H, J = 8.9 Hz, H2), 5.05 (m, 1H, H6).

(2*R*)-methyl *N*-acetyl-4-ethyl-5-hydroxyprolinate **12**: ¹H NMR. δ 1.08 (t, 3H, J = 7.5 Hz, CH₃CH₂), 1.31–1.73 (m, 3H, CH₃CH₂, H4), 2.15 (s, 3H, COCH₃), 2.37–2.47 (m, 2H, H3), 3.76 (s, 3H, COOCH₃), 4.44–4.53 (m, 1H, H2), 5.29 (m, 1H, H5).

The CDCl₃ solutions of **11** and **12** on storing for several hours underwent dehydration to give (2R)-methyl *N*-acetyl-5-methyl-5,6-didehydropipecolate **9a** in 30% yield and

Similar reactions were carried out by varying ligand, pressure, temperature and reaction time. The results are summarised in Table 2.

Reaction of (2S)-methyl 2-acetamidopent-4-enoate 5b. (2S)-Methyl N-acetyl-5,6-didehydropipecolate **9b** and (2S)-methyl N-acetyl-4-methyl-4,5-didehydroprolinate **10b**. The (2S)-pent-4-enoate **5b** (74 mg, 0.43 mmol), rhodium(II) acetate dimer (1.9 mg, 4.3 µmol) and BIPHEPHOS (6.8 mg, 8.6 µmol) in deoxygenated benzene (10 mL) were reacted with CO/H₂ (80 psi) at 80 °C for 72 h to give a brown oil (80 mg). The ¹H NMR spectrum indicated the pipecolate **9b** and the prolinate **10b** were present in a 66:34 ratio respectively. The two compounds were separated using column chromatography (3:1 of ethyl acetate:light petroleum).

(2*S*)-Methyl *N*-acetyl-5,6-didehydropipecolate **9b** was isolated as clear oil (38 mg, 48%), ($R_{\rm f}$ 0.5). HPLC: (*S*), $t_1 = 9.3$ min (*R*), $t_2 = 26.5$ min; ee 99% (*S*). IR (neat): 3468, 1744, 1674, 1645, 1417, 1383, 1347, 1208, 1045 cm⁻¹. ¹H NMR: δ [minor rotamer in brackets] 1.80–2.12 (m, 3H, H3, H4a), 2.23 (s, 3H, [2.13, s], COCH₃), 2.35–2.41 (m, 1H, H4b), 3.73 (s, 3H, [3.75, s], COOCH₃), 4.97 (m, 1H, [5.00–5.10, m], H5), 5.24 (m, 1H, [4.65–4.66, m], H2), 6.63 (d, 1H, *J* 8.6 Hz, H6). ¹³C NMR: δ [minor rotamer in brackets] 18.9 [18.6] (C3), 21.5 (COCH₃), 23.3 [23.9] (C4), 51.7 [55.7] (C2), 52.3 [52.6] (COOCH₃), 107.1 [107.0] (C5), 125.1 [123.2] (C6), 168.5, 171.0 (C1, CONH). Calc. for C₉H₁₃NO₃: C, 58.99; H, 7.16; N, 7.65. Found: C, 59.01; H, 7.12; N, 7.60%. [α]_D²⁰ –64° (*c* 0.016, CH₃Cl).

(2*S*)-Methyl *N*-acetyl-4-methyl-4,5-didehydroprolinate **10b** was isolated as a colourless oil (21 mg, 27%), (R_f 0.3). HPLC: (*S*), $t_1 = 12.2$ min; (*R*), $t_2 = 26.2$ min; ee 99% (*S*). IR (neat): 3296, 1746, 1654, 1542, 1375, 1208 cm⁻¹. ¹H NMR: δ 1.74 (s, 3H, CH₃C4), 2.14 (s, 3H, COCH₃), 2.50 (m, 1H, H3a), 2.94 (m, 1H, H3b), 3.76 (s, 3H, COOCH₃), 4.82 (dd, 1H, J = 11.7, 5.1 Hz, H2), 6.22 (q, 1H, J = 1.8 Hz, H5). ¹³C NMR: δ 13.8 (CH₃C4), 21.9 (COCH₃), 38.3 (C3), 52.8 (COOCH₃), 58.5 (C2), 120.2 (C4), 124.3 (C5), 165.9, 171.9 (C1, CONH). HRMS (ESI⁺, MeOH): calc. for (C₉H₁₃NO₃ + Na)⁺ m/z 206.0793, found, 206.0787 (M + Na)⁺.

Reaction of **5b** (40 mg, 0.23 mmol) using BIPHEPHOS at 80 °C, 80 psi for 20 h gave a crude oil containing *ca.* 50% of the pent-3-enoate **13** and the cyclic compounds **9b** and **10b** in a ratio of 78:22. (2*S*,3*E*)-Methyl 2-acetamidopent-3-enoate **13** was isolated as a clear oil, (R_f 0.4). IR (neat): 3283, 1746, 1655, 1542, 1375 cm⁻¹. ¹H NMR: δ 1.70 (ddd, 3H, J = 6.5, 1.7, 1.2 Hz, H5), 2.03 (s, 3H, COCH₃), 3.75 (s, 3H, COOCH₃), 5.03 (m, 1H, H2), 5.46 (ddq, 1H, J = 15.3, 6.4, 1.7 Hz, H4), 5.77 (m, 1H, H3), 6.16 (bs, 1H, NH). ¹³C NMR: δ 18.2 (C5), 23.5 (COCH₃), 53.0, 54.5 (C2, COOCH₃), 125.2, 130.3 (C3, C4), 169.6, 171.8 (C1, CONH). HRMS (ESI⁺, MeOH): calc. for (C₈H₁₃NO₃ + H)⁺ m/z 172.0974, found, 172.0964 (M + H)⁺.

Similar reactions were carried out by varying ligand, pressure, temperature and reaction time. The results are summarised in Table 2.

Reaction of (2*R***)-methyl 2-acetamidohept-6-enoate 5c.** (2*R*)-Methyl 2-acetamido-7-formylheptanoate 14 and (2*R*)-methyl 2acetamido-6-formylheptanoate 15. The (2*R*)-hept-4-enoate 5c (70 mg, 0.36 mmol), rhodium(II) acetate dimer (1.6 mg, 3.6 µmol) and triphenylphosphine (1.9 mg, 7.2 µmol) in deoxygenated benzene (10 mL) were reacted with CO/H₂ (400 psi) at 80 °C for 20 h to give a brown oil (80 mg). The ¹H and ¹³C NMR spectra indicated the two aldehydes 14 and 15 were present in a 50:50 ratio. The aldehydes were partially separated using radial chromatography (ethyl acetate:light petroleum, The (2*R*)-heptanoate **14** was isolated as a yellow oil (28 mg, 34%), ($R_{\rm f}$ 0.86). IR (neat): 3296, 2938, 1744, 1657, 1542, 1438, 1438, 1375, 1211, 1167 cm⁻¹. ¹H NMR: δ [minor rotamer in brackets] 1.20–1.37 (m, 4H, H4, H5), 1.55–1.69 (m, 2H, H6), 1.77–1.83 (m, 2H, H3), 2.00 (s, 3H, [2.02, s], COCH₃), 2.41 (td, 2H, J = 7.2, 1.7 Hz, H7), 3.75 (s, 3H, [3.72, s], COOCH₃), 4.62 (m, 1H, H2), 6.14 (bs, 1H, NH), 9.73 (t, 1H, J = 1.7 Hz, [9.75, m], CHO). ¹³C NMR: δ 24.5 (COCH₃), 22.1 (C6), 25.3 (C4), 29.0 (C5), 32.6 (C3), 44.0 (C7), 52.3, 52.7 (C2, COOCH₃), 170.0, 173.2 (C1, CONH), 202.6 (CHO). HRMS (EI, MeOH): calc. for (C₁₁H₁₉NO₄–COCH₃) m/z 186.1130, found, 186.1133 (M–COCH₃).

The (2*R*)-heptanoate **15** was obtained as a yellow oil (24 mg, 29%), ($R_{\rm f}$ 0.95) containing 20% of **14**. IR (neat): 1740, 1656, 1545, 1438, 1375, 1212, 1178 cm⁻¹. ¹H NMR: δ (1:1 mixture of two diastereoisomers) 1.10 (d, 3H, J = 7.0 Hz, H7), 1.23–1.46 (m, 3H, H4, H5a), 1.58–1.90 (m, 3H, H3, H5b), 2.03 (s, 3H, COCH₃), 2.24–2.38 (m, 1H, H6), 3.75 (s, 3H, COOCH₃), 4.63 (m, 1H, H2), 6.21 (d, 1H, J = 7.8 Hz, NH), 9.60 (m, 1H, CHO).† ¹³C NMR: δ (1:1 mixture of two diastereoisomers) 13.8 (C7), 23.0 (C4), 30.2 (C5), 32.9 (C3), 46.5 (C6), 52.2, 52.8 (C2, COOCH₃), 170.1, 173.2 (C1, CONH), 204.9 (CHO). HRMS (EI, MeOH): calc. for (C₁₁H₁₉NO₄–COCH₃) m/z 186.1130, found, 186.1133 (M–COCH₃). A similar reaction was carried out using **5c** (37 mg), rhodium(II) acetate dimer (0.9 mg, 8.4 µmol) and BIPHEPHOS (3.0 mg, 3.8 µmol) also gave a 1:1 mixture of the aldehydes **14** and **15**.

One-pot tandem hydrogenation and hydroformylation reactions

Reactions were carried out in a 100 mL Parr autoclave (see previous conditions used for hydroformylation reactions).

Two catalyst system

The ratio of substrate:Rh-DuPHOS:[Rh(OAc)₂]₂:BIPHE-PHOS or PPh₃ was 100:1:1:2; CO/H₂ (1:1 molar mixture).

Reaction of (2Z,4E)-methyl 2-acetamidohexa-2,4-dienoate 1a. The (2Z,4E)-hexa-2,4-dienoate 1a (50 mg, 0.27 mmol), [(COD)Rh-(S,S)-Et-DuPHOS]OTf, rhodium(II) acetate dimer (1.2 mg, 2.7 µmol) and triphenylphosphine (1.4 mg, 5.4 µmol) were dissolved in deoxygenated benzene (10 mL) as described previously. The autoclave was charged with hydrogen (90 psi) and the mixture was stirred for 2 h. The hydrogen was vented and the autoclave was pressurized to 400 psi of CO/H_2 and heated to 80 °C for 20 h to give a brown oil (50 mg). The 1 H NMR spectrum of the crude oil showed two compounds, the pipecolate 9a and the prolinate 10a in a 56:44 ratio respectively. The compounds were separated as described previously. The (2S)-pipecolate 9a was isolated as a clear oil (27 mg, 51%). HPLC showed the ee as 95% (S). The (2S)-prolinate 10a was obtained as a clear oil (16 mg, 30%). HPLC showed the ee as 99% (S).

Reaction of (2Z)-methyl 2-acetamidopenta-2,4-dienoate 1b. A solution of the (2Z)-penta-2,4-dienoate **1b** (40 mg, 0.24 mmol), [(COD)Rh-(*S*,*S*)-Et-DuPHOS]OTf, rhodium(II) acetate dimer (1.0 mg, 2.4 µmol) and BIPHEPHOS (3.4 mg, 5.4 µmol) in deoxygenated benzene (10 mL) was reacted with hydrogen at 30 psi for 3 h. The hydrogen was vented and the autoclave was pressurized to 80 psi of CO/H₂ and heated to 80 °C for 72 h. After work up, the ¹H NMR spectrum of the crude oil (40 mg) showed the pipecolate **9b** and the prolinate **10b** in a

67:33 ratio respectively as well as the isomerised alkene **13** (*ca.* 25%). The compounds were separated as described previously. The (2S)-pipecolate **9b** was isolated as a clear oil (17 mg, 39%). HPLC showed the ee as 97% (S). The (2S)-prolinate **10b** was obtained as a colourless oil (9 mg, 21%). HPLC showed the ee as 99% (S).

Reaction of (2Z)-methyl 2-acetamidohepta-2,6-dienoate 1c. (2S)-Methyl N-acetyl-6-methyl-6,7-didehydroazepan-1-yl-2carboxylate 17 and (2S)-methyl N-acetyl-5-ethyl-5,6-didehydropipecolate 18. The (2Z)-hepta-2,6-dienoate 1c (40 mg, 0.20 mmol), [(COD)Rh-(S,S)-Et-DuPHOS]OTf, rhodium(II) acetate dimer (1.1 mg, 2.5 µmol) and BIPHEPHOS (3.9 mg, 5.0 µmol) in deoxygenated benzene (10 mL) were reacted with hydrogen at 30 psi for 2 h. The hydrogen was vented and the autoclave was pressurized to 800 psi of CO/H₂ and heated to 150 °C for 72 h. After work up, the ¹H NMR spectrum of the crude oil (40 mg) showed three compounds, (2S)-methyl N-acetyl-6-methyl-6,7-didehydroazepan-1-yl-2-carboxylate 17, (2S)-methyl N-acetyl-5-ethyl-5,6-didehydropipecolate 18 and (2S)-methyl 2-acetamidoheptanoate 6c in a 13:13:74 ratio respectively. Purification using radial chromatography (ethyl acetate:light petroleum = 1:1) gave a sample of the cyclic products 17 and 18 in a ca. 1:1 ratio as a yellow oil (10 mg, 24%), $(R_{\rm f}0.33)$. HRMS (ESI⁺, MeOH): calc. for $(C_{11}H_{17}NO_3 + Na)^+$ m/z 234.1106, found, 234.1097 (M + Na)⁺

(2*S*)-Methyl 2-acetamido-6-methyl-6,7-didehydroazepan-1yl-2-carboxylate **17**, ¹H NMR: δ 1.6–2.2 (m, 6H, H3, H4, H5), 1.74 (d, 3H, J = 1.3 Hz, CH₃), 2.09 (s, 3H, COCH₃), 3.70 (s, 3H, COOCH₃), 5.14 (dd, 1H, J = 7.4, 5.2 Hz, H2), 6.10 (s, 1H, H7).

(2*S*)-Methyl *N*-acetyl-5-ethyl-5,6-didehydropipecolate **18**,¹H NMR: δ 1.03 (t, 3H, J = 7.4 Hz, CH₃CH₂), 1.78–1.90 (m, 1H, H3), 1.93–2.09 (m, 4H, H4, CH₃CH₂), 2.23 (s, 3H, COCH₃); 2.33–2.40 (m, 1H, H3); 3.71 (s, 3H, COOCH₃); 5.20 (m, 1H, H2); 6.39 (bs, 1H, H6).

(2*S*)-Methyl 2-acetamidoheptanoate **6c**, (R_f 0.44) was isolated as a yellow oil. IR (neat) 3311, 1738, 1656 cm⁻¹. ¹H NMR: δ 0.88 (t, 3H, J = 6.6 Hz, H7), 1.21–1.41 (m, 6H), 1.59–1.71 (m, 1H), 1.78–1.97 (m, 1H), 2.03 (s, 3H, COCH₃), 3.75 (s, 3H, COOCH₃), 4.61 (m, 1H, H2), 6.19 (bd, 1H, J 7.2 Hz, NH). ¹³C NMR: δ 14.3 (C7), 22.8 (C4), 23.6 (COCH₃), 25.2 (C5), 31.7, 32.9 (C3, C6), 52.5, 52.7, C2, COOCH₃), 169.9, 173.4 (C1, CONH). MS (ESI⁺, MeOH): m/z 224.3 (M + Na)⁺.

One catalyst system

The ratio of substrate:Rh-DuPHOS was 100:1; CO/H_2 (1:1 molar mixture).

Reaction of (2Z,4E)-methyl 2-acetamidohexa-2,4-dienoate 1a. The (2Z,4E)-hexa-2,4-dienoate **1a** (40 mg, 0.22 mmol) and [(COD)Rh-(*S,S*)-Et-DuPHOS]OTf in deoxygenated benzene (10 mL) were reacted with hydrogen at 90 psi for 2 h. The hydrogen was vented and the autoclave was pressurized to 800 psi of CO/H₂ and heated to 150 °C for 72 h. After work up, the ¹H NMR spectrum of the crude oil (40 mg) showed only the pipecolate **9a**. Purification using chromatography (ethyl acetate:light petroleum = 3:1) gave the (2S)-pipecolate **9a** as a clear oil (25 mg, 58%). HPLC showed the ee as 96% (S).

A similar reaction was carried out at 400 psi, 80 °C for 20 h gave a mixture of **9a** and **10a** (ratio 83:17) as well as *ca*. 15% of the aldehydes **7a** and **8a** (¹H NMR: δ 9.76).

Reaction of (2Z)-methyl 2-acetamidopenta-2,4-dienoate 1b. The (2Z)-penta-2,4-dienoate **1b** (50 mg, 0.30 mmol) and [(COD)Rh-(S,S)-Et-DuPHOS]OTf in deoxygenated benzene (10 mL) were reacted with hydrogen at 30 psi for 3 h. The hydrogen was vented and the autoclave was pressurized to 400 psi of CO/H₂ and heated to 80 °C for 72 h. After work

[†] At 400 MHz using a Bruker-DRX spectrometer, all chemical shifts were the same except for the CHO peaks at δ 9.59 (d, 1H, J = 1.9 Hz) and 9.60 (d, 1H, J = 1.8 Hz). CHO.

up, the ¹H NMR spectrum of the crude oil (40 mg) showed the pipecolate 9b and the prolinate 10b in a 54:46 ratio respectively. The compounds were separated as described previously. The (2S)-pipecolate 9b was isolated as a clear oil (22 mg, 40%). HPLC showed the ee as 94% (S). The (2S)-prolinate 10b was isolated as an oil (28 mg, 51%). HPLC showed the ee as 99% (S).

A similar reaction was carried out at 80 psi, 80 °C for 72 h gave 9b and 10b in a 74:26 ratio respectively as well as ca. 40% of the isomerised alkene 13. The spectral data were consistent with those described above.

Reaction of (2Z)-methyl 2-acetamidohepta-2,6-dienoate 1c. The (2Z)-hepta-2,6-dienoate 1c (40 mg, 0.20 mmol) and [(COD)Rh-(S,S)-Et-DuPHOS]OTf in deoxygenated benzene (10 mL) were reacted with hydrogen at 30 psi for 2 h. The hydrogen was vented and the autoclave was pressurized to 800 psi of CO/H₂ and heated to $150 \,^{\circ}$ C for 72 h. After work up, the ¹H NMR spectrum of the crude oil (40 mg) showed the (2S)-methyl N-acetyl-5-ethyl-5,6-didehydropipecolate 18 and (2S)-methyl 2-acetamidoheptanoate 6c in a 33:67 ratio respectively.

The pipecolate 18 was isolated using radial chromatography (ethyl acetate:light petroleum = 1:1) as a yellow oil (5 mg, 12%), ($R_{\rm f}$ 0.35). IR (neat) 3339, 2953, 1744, 1656, 1406, 1378, 1311, 1205, 1172, 1033 cm⁻¹. ¹H NMR: δ 1.03 (t, 3H, J = 7.4 Hz, CH₃CH₂), 1.78–1.90 (m, 1H, H3), 1.93–2.09 (m, 4H, H4, CH₃CH₂), 2.23 (s, 3H, COCH₃); 2.33–2.40 (m, 1H, H3); 3.71 (s, 3H, COOCH₃); 5.20 (m, 1H, H2); 6.39 (bs, 1H, H6). ¹³C NMR: δ 12.7 (CH₃CH₂), 21.6 (COCH₃), 22.6 (C4), 23.7 (C3), 28.4 (CH₃CH₂), 51.7 (C2), 52.6 (COOCH₃), 119.1 (C6), 121.7 (C5), 168.3, 171.2 (C1, CONH). HRMS (ESI⁺, MeOH): calc. for $(C_{11}H_{17}NO_3 + Na)^+ m/z$ 234.1106, found, $234.1097 (M + Na)^+$.

Cyclic amino acids

(2R)-Methyl N-acetylpipecolate 20. (2R)-Methyl N-acetyl-5,6-didehydropipecolate 9a (prepared by hydrogenation of 5a using Rh-(R,R)-Et-DuPHOS) (59 mg, 0.32 mmol) was dissolved in methanol (5 mL) and added to a Fischer-Porter tube followed by palladium on charcoal (10%). The mixture was hydrogenated at 90 psi for 18 h. The catalyst was removed by filtration through a Celite pad and the filtrate was concentrated in vacuo to give the ester 20 as an oil (50 mg, 84%). ¹H NMR:³² δ [minor rotamer in brackets] 1.25–1.87 (m, 5H), 2.14 (s, 3H, [2.08, s]), 2.21-2.28 (m, 1H), 3.28 (m, 1H, [2.61, m]), 3.71-3.78 (m, 1H, [4.58, m]), 3.73 (s, 3H, [3.77, s]), 5.39 (m, 1H, [4.53, m]). ¹³C NMR: δ [minor rotamer in brackets] 21.0 [20.9], 21.8 [21.6] (COCH₃), 25.4 [24.6], 26.7 [27.4], 44.3 [39.3] (C6), 51.8 [52.6] (COOCH₃), 52.3 [56.9] (C2), 170.5 [170.3] and 171.8 [171.2] (C1, CONH). HRMS (ESI⁺, MeOH): calc. for $(C_{10}H_{15}NO_3 + Na)^+ m/z$ 208.0949, found, 208.0943 $(M + Na)^{+}$.

(2R)-Pipecolinic acid hydrochloride 21. (2R)-Methyl Nacetylpipecolate 20 (50 mg, 0.27 mmol) was refluxed in 6 M HCl overnight. After work up, the solution was concentrated to give the salt **21** as white solid (40 mg, 89%) mp 260–264 °C (lit.²⁶ 256–257 °C). The ¹H and ¹³C NMR spectra in D₂O were consistent with literature data.³³ ¹H NMR: δ (CD₃OD) 1.56-1.78 (m, 3H), 1.80-1.94 (m, 2H), 2.26 (m, 1H), 3.01 (m, 1H), 3.43 (m, 1H), 3.77 (m, 1H). HRMS (ESI⁺, MeOH): calc. for $(C_6H_{11}NO_2 + Na)^+ m/z$ 152.0688, found, 152.0680 $(M + Na)^+$. $[\alpha]_D^{20} + 10^\circ$ (c 0.002, H₂O) (lit.²⁶ for (2R)-**21**, $[\alpha]_D^{20} + 10.8^\circ$ (c 2, H₂O)).

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