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

Received (in New Haven, CT, USA) 6th September 2002, Accepted 18th October 2002
First published as an Advance Article on the web 3rd January 2003

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

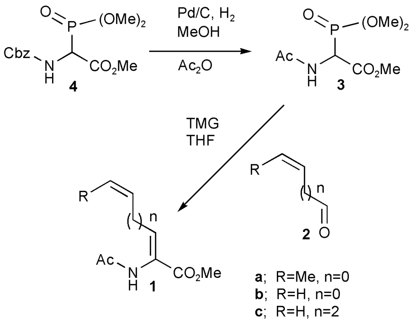
There is a growing trend in the pharmaceutical and fine chemicals industries towards replacing classical organic synthesis with cleaner catalytic alternatives. Attention to E factor,[1] the amount of waste generated per kilo of product,[2] has driven chemists to reduce or eliminate the use and generation 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 economy[3] 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 alkaloids[6] (piperidines) and kainic acid[7] (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 hydroformylation–Knoevenagel–hydrogenation,[9] hydroformylation–Wittig,[10] isomerization–hydroformylation,[11] hydroformylation–conjugate addition[12] and isomerisation–carbonylation[13] 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

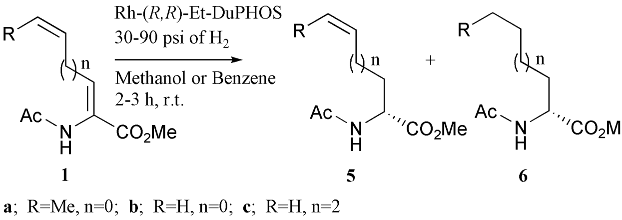
The hydrogenation precursors, the dienamide esters **1**, were readily accessible by reaction of unsaturated aldehydes **2** with the phosphonate **3**[14,15] (Scheme 1). The Cbz-protected phosphonate **4**[15] was prepared in 81% yield and converted quantitatively into the N-acetyl-protected phosphonate **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 olefination[18] 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]



Scheme 1

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



Scheme 2

DOI: 10.1039/b209087m

Table 1 Rh-catalysed asymmetric hydrogenation of dienamide esters **1**[a]

Entry	Substrate	R	n	Pressure/ psi	Time/ h	Product	Ratio[b] **5**:**6**	Yield (%)[c]	% 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**	H	0	30	3	**5b**	95:5	88	95
4	**1b**	H	0	30	3	**5b**	95:5	90	76[f]
5	**1b**	H	0	30	3	**5b**	95:5	90	95[e]
6	**1c**	H	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 ^{1}H 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.

Table 2 Rh-catalysed hydroformylation of hydrogenated enamides **5a**; R = Me and **5b**; R = H[a]

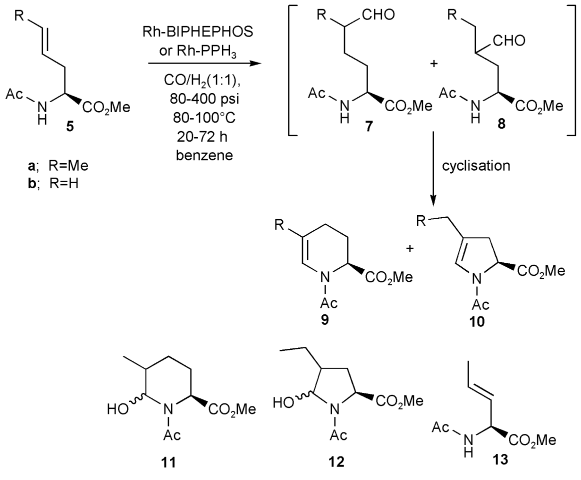
Entry	R	Catalyst system	CO/ H_2/psi	T/°C	Time/ h	Product ratio **9**:**10**	Yield (%)[b]	% ee[c] **9**/**10**
7	Me	A	400	80	20	67:33	45	91/98
8	Me	B	400	80	20	100:0	37[d]	—
9	Me	B	400	100	72	91:9	81	97/98
10	Me	A	400	80	20	80:20	47[e]	—
11	H	A	400	80	72	50:50	73	—/87
12	H	B	400	80	20	63:37	66	88/—
13	H	B	100	80	20	71:29	54[f]	—/87
14	H	B	80	80	20	78:22	[g]	—
15	H	B	80	80	72	66:34	75	99/99

[a] Reaction conditions: substrate:$[Rh(OAc)_2]_2$:PPh_3 or BIPHEPHOS ratio = 100:1:2 in benzene (5–10 mL), A = Rh-PPh_3 and B = Rh-BIPHEPHOS. 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 Chiralcel® OD); — Signifies that enantiomeric excess (ee) 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**.

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 H_2) 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 H_2) 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 BIPHEPHOS[23] 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/PPh_3 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 PPh_3 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 PPh_3 as ligand, the initial product contained the amidals **11** and **12** which dehydrated on standing in $CDCl_3$ to give the enamides **9a** and **10a** (entry 10). Similar amidals have been isolated by Ojima and coworkers.[20,22]

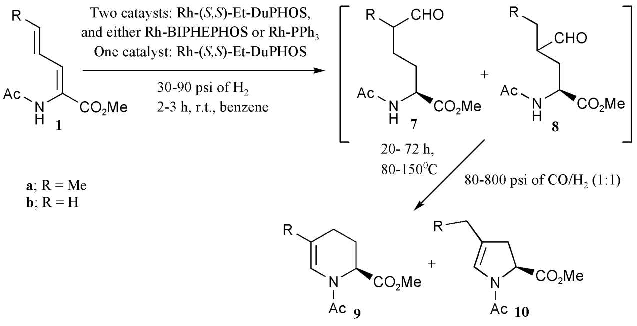


Scheme 3

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 PPh_3 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 ligand[23] (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-PPh_3 catalysts.



Scheme 4

After the low pressure hydrogenation was complete, the gas was vented and replaced by a 1:1 CO/H_2 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-PPh_3 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).

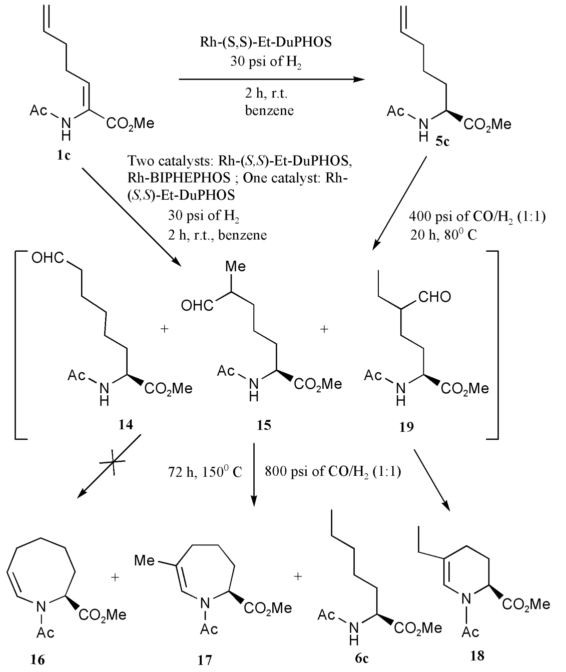
The possibility of using Rh-DuPHOS as a catalyst for both reactions was investigated. This catalyst has not been used previously for hydroformylation reactions. Reactions of dienamide substrates **1a** and **1b** using Rh-Et-DuPHOS, initially under hydrogenation conditions and then under hydroformylation 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-PPh_3 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 hydroformylated using the Rh-PPh_3 and Rh-BIPHEPHOS systems and gave the aldehydes **14** and **15** (entries 22 and 23). No cyclic material was observed.

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	T/ °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	H	B + C	80	80	72	67:33	60[d]	95/95
18	Me	C	400	80	20	83:17	35[e]	99/99
19	Me	C	800	150	72	100:0	58	96/—
20	H	C	80	80	72	74:26	[f]	—
21	H	C	400	80	72	54:46	91	95/99

[a] Reaction conditions: substrate:Rh-Et-DuPHOS:$[Rh(OAc)_2]_2$:PPh_3 or BIPHEPHOS ratio = 100:1:1:2 in benzene (5–10 mL) with H_2 (90 psi, 2 h for **1a** and 30 psi, 3 h for **1b**) at ambient temperature followed by CO/H_2 (1:1 ratio), A = Rh-PPh_3, 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**.



Scheme 5

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.

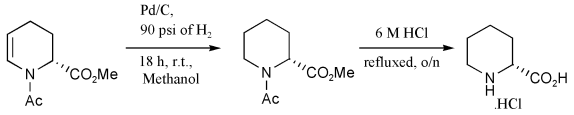
A one-pot reaction using only Rh-DuPHOS as catalyst under the same conditions again gave predominantly the saturated compound **6c** (Table 4, entry 25). Chromatography led to the isolation of the 6-ring compound **18** in 12% yield. The difficulty associated with the formation of 7- and 8-membered rings 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**	A	400	80	20	[d]	—
23	**5c**	B	400	80	20	[e]	—
24	**1c**	B + C	800	150	72	50:50[f]	12
25	**1c**	C	800	150	72	0:100[g]	24

[a] Reaction conditions: substrate:Rh-Et-DuPHOS:$[Rh(OAc)_2]_2$:PPh_3 or BIPHEPHOS ratio = 100:1:1:2 in benzene (5–10 mL) with 30 psi of H_2 for 2 h at ambient temperature followed by CO/H_2 (1:1 ratio), A = Rh-PPh_3, 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**.



9b 20 21

Scheme 6

rotation, $[\alpha]_D$ +10° was almost identical to a literature $[\alpha]_D$ +10.8° 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

^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz respectively with a Varian Mercury 300 Q Spectrometer in $CDCl_3$ and referenced to Me_4Si unless otherwise stated. ^{31}P NMR spectra were recorded at 121.5 MHz on a Bruker AM-300 spectrometer in deuterated solvents with 85% phosphoric acid (H_3PO_4) 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-((2*R*,5*R*)-Et-DuPHOS)]OTf and [(COD)Rh-((2*S*,5*S*)-Et-DuPHOS)]OTf were used as supplied from Strem Chemicals. $[Rh(OAc)_2]_2$ and BIPHEPHOS[22] were prepared by Eva M. Campi. PPh_3 was obtained from Aldrich. H_2 and 1:1 molar mixture of CO/H_2 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 Schmidt[15] from methyl *N*-benzyloxycarbonyl-2-methoxyglycinate[16,17] (23.0 g, 90.81 mmol) as a white solid, (24.33 g, 81%); mp 77–78 °C (lit.[15] 80 °C). ^{1}H NMR: δ [minor rotamer in brackets] 3.77–3.83 (m, 9H, $COOCH_3$, 2 × CH_3OP), 4.93 (dd, 1H, J = 22.4, 9.3 Hz, [5.12, bd, J ~8.2 Hz], H2), 5.13 (d, 1H, J = 12.2 Hz) and 5.15 (d, 1H, J = 12.1 Hz, CH_2O), 5.77 (bd, 1H, J ~8.2 Hz, [6.21, bs], NH), 7.32–7.40 (m, 5H, ArH). ^{13}C NMR: δ [minor rotamer in brackets] 52.4 (d, J = 148.0 Hz, [73.9, s], C2), 53.7 [53.5] ($COOCH_3$), 54.4 (d, J = 6.9 Hz, CH_3OP), 54.5 (d, J = 6.6 Hz, CH_3OP), 67.9 [67.7] (CH_2O), 128.4, 128.5, 128.8 (ArCH), 136.0 (C1′), 155.8 [155.9] (CONH), 167.3 [170.0] (C1). ^{31}P 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). ^{1}H NMR: δ 2.06 (s, 3H, $COCH_3$), 3.79–3.81 (m, 9H, $COOCH_3$, 2 × CH_3OP), 5.24 (dd, 1H, J = 22.3, 8.5 Hz, H2), 6.74 (d, 1H, J = 8.6 Hz, NH). ^{13}C NMR: δ 23.3 ($COCH_3$), 49.3 (d, J = 147.2 Hz, C2), 53.7 ($COOCH_3$), 54.3 (d, J = 6.6 Hz, CH_3OP), 54.6 (d, J = 6.3 Hz, CH_3OP), 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 ^{1}H and ^{13}C NMR spectra indicated that the crude oil was a mixture of 4-pentenal **2c** and starting material (δ 3.62, t, CH_2) 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**. ^{1}H 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). ^{13}C 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]

(2*Z*,4*E*)-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 CH_2Cl_2 (20 mL), washed with 1 M HCl (2 × 10 mL), 1 M $CuSO_4$(2 × 10 mL), saturated $NaHCO_3$ (2 × 10 mL) and 1 M NaCl (10 mL). The organic layer was dried with $MgSO_4$ 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). ^{1}H NMR: δ 1.88 (d, 3H, $J = 5.2$ Hz, H6), 2.16 (s, 3H, $COCH_3$), 3.17 (s, 3H, $COOCH_3$), 6.16–6.20 (m, 2H, H4, H5), 6.90 (bs, 1H, NH), 7.08 (d, 1H, $J = 10.1$ Hz, H3). ^{13}C NMR: δ 19.3 (C6), 23.6 ($CO\mathbf{C}H_3$), 52.6 ($COO\mathbf{C}H_3$), 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 $(M + Na)^+$.

(2*Z*)-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 °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 (2*Z*)-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}. ^{1}H NMR: δ 2.14 (s, 3H, $COCH_3$), 3.79 (s, 3H, $COOCH_3$), 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). ^{13}C NMR: δ 23.8 ($CO\mathbf{C}H_3$), 52.8 ($COO\mathbf{C}H_3$), 132.1, 132.9 (C3, C4), 123.7 (C2), 125.2 (C5), 165.6, 168.8 (C1, CONH). Calc. for $C_8H_{11}NO_3$: C, 56.78; H, 6.54; N, 8.28. Found: C, 56.66; H, 6.67; N, 8.29%.

(2*Z*)-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 (2*Z*)-dienoate **1c** as a white solid (0.22 g, 38%), (R_f 0.24); mp 44–45 °C (lit.[15] 44 °C). ^{1}H NMR: δ 2.10 (s, 3H, $COCH_3$), 2.16–2.29 (m, 4H, H4, H5), 3.75 (s, 3H, $COOC\mathbf{H}_3$), 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). ^{13}C NMR: δ 23.2 ($CO\mathbf{C}H_3$), 28.0 (C4), 32.3 (C5), 52.3 ($COO\mathbf{C}H_3$), 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 ^{1}H 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, CH_3), 1.22–1.39 (m, CH_2)] in a 94:6 ratio respectively. IR (neat) 3284, 2954, 1747, 1658, 1547, 1437, 1375, 1217, 1142, 968 cm^{-1}. ^{1}H NMR: δ 1.67 (ddt, 3H, $J = 6.4$, 1.7, 1.1 Hz, H6), 2.03 (s, 3H, $COCH_3$), 2.43–2.51 (m, 2H, H3), 3.75 (s, 3H, $COOCH_3$), 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). ^{13}C NMR: δ 18.3 (C6), 23.4 ($CO\mathbf{C}H_3$), 35.6 (C3), 52.3, 52.6 (C2, $COO\mathbf{C}H_3$), 124.6, 130.1 (C4, C5), 169.8, 172.6 (C1, CONH). MS (ESI$^+$, MeOH): m/z 207.9 $(M + Na)^+$. $[\alpha]_D^{22}$ −55° (*c* 1.18, $CHCl_3$) containing 6% of **6a** (lit.[14] $[\alpha]_D^{20}$ −57.2° (*c* 1.18, $CHCl_3$) containing < 2% of **6a**).

(2*R*)-Methyl 2-acetamidopent-4-enoate 5b. Hydrogenation of (2*Z*)-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 ^{1}H NMR spectrum indicated the (2*R*)-pent-4-enoate **5b** and the fully saturated compound, (2*R*)-methyl 2-acetamidopentanoate **6b** [δ 0.93 (t, $J = 7.3$ Hz, CH_3), 1.25–1.44 (m, CH_2)] 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}. ^{1}H NMR: δ 2.00 (s, 3H, $COCH_3$), 2.42–2.61 (m, 2H, H3), 3.72 (s, 3H, $COOCH_3$), 4.66 (m, 1H, H2), 5.09 (d, 1H, $J = 16.2$ Hz, $H5_{(Z)}$), 5.10 (d, 1H, $J = 11.1$ Hz, $H5_{(E)}$), 5.65 (m, 1H, H4), 6.14 (bs, 1H, NH). ^{13}C NMR: δ 23.4 ($CO\mathbf{C}H_3$), 51.8, 52.5 (C2, $COO\mathbf{C}H_3$), 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° (*c* 0.047, CH_3Cl) containing 5% of **6b**.

(2*R*)-Methyl 2-acetamidohept-6-enoate 5c. Hydrogenation of (2*Z*)-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 ^{1}H NMR spectrum indicated the (2*R*)-hept-6-enoate **5c** and the fully saturated compound, (2*R*)-methyl 2-acetamidoheptanoate **6c** [(δ 0.88 (t, $J = 6.6$ Hz, CH_3)] 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}. ^{1}H NMR: δ 1.26–1.53 (m, 2H, H4), 1.58–1.91 (m, 2H, H3), 2.03 (s, 3H, $COCH_3$), 2.06–2.10 (m, 2H, H5), 3.75 (s, 3H, $COOCH_3$), 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). ^{13}C NMR: δ 23.5 ($CO\mathbf{C}H_3$), 24.8 (C4), 32.2 (C3), 33.5 (C5), 52.4, 52.7 (C2, $COO\mathbf{C}H_3$), 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–$COCH_3$). $[\alpha]_D^{22}$ −60° (*c* 0.15, CH_3Cl) 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 (2*R*,4*E*)-methyl 2-acetamidohex-4-enoate 5a. *(2R)-Methyl N-acetyl-5-methyl-5,6-didehydropipecolate* **9a** *and (2R)-methyl N-acetyl-4-ethyl-4,5-didehydroprolinate* **10a**. (2*R*,4*E*)-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/H_2 (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 ^{13}C 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_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], CH_3C5), 1.80–2.00 (m, 3H, H3, H4a), 2.22 (s, 3H, [2.11, s], $COCH_3$), 2.37 (m, 1H, H4b), 3.71 (s, 3H, [3.76, s], $COOCH_3$), 5.23 (m, 1H, [4.60, bs], H2), 6.40 (s, 1H, [7.04, s], H6). ^{13}C NMR: δ [minor rotamer in brackets] 21.4 [21.2] ($\mathbf{C}H_3C5$), 21.75 [21.85] ($CO\mathbf{C}H_3$), 23.7 [24.2] (C3), 24.7 [24.3] (C4), 51.3 [53.1] (C2), 52.7 [55.4] ($COO\mathbf{C}H_3$), 116.1 [116.7] (C5), 120.1 [118.4] (C6), 168.2, 171.3 (C1, CONH). Calc. for $C_{10}H_{14}NO_3$: C, 60.88; H, 7.67; N, 7.10. Found: C, 60.74; H, 7.69; N, 6.96%. $[\alpha]_D^{20}$ +138° (*c* 0.034, CH_3Cl).

(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), $t_1 = 11.0$ min; (R), $t_2 = 18.7$ min; ee 98% (*R*). IR (neat): 2858, 1750, 1647, 1438, 1208 cm^{-1}. ^1H NMR: δ 1.08 (t, 3H, $J = 7.5$ Hz, $\mathbf{CH_3}CH_2$), 2.03–213 (m, 2H, $CH_3\mathbf{CH_2}$), 2.15 (s, 3H, $COCH_3$), 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, $COOCH_3$), 4.82 (dd, 1H, $J = 11.7$, 5.2 Hz, H2), 6.19–6.21 (m, 1H, H5). ^{13}C NMR: δ 12.5 ($\mathbf{C}H_3CH_2$), 21.8 (C3), 21.9 ($COCH_3$), 36.7 ($CH_3\mathbf{C}H_2$), 52.7, 58.7 (C2, $COOCH_3$), 122.9 (C5), 126.4 (C4), 166.0, 171.9 (C1, CONH). HRMS (EI, MeOH): calc. for $C_{10}H_{15}NO_3$ *m/z* 197.1052, found 197.1046 (M). $[\alpha]_D^{20}$ +114° (*c* 0.028, CH_3Cl).

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/H_2 for 20 h gave a brown oil (64 mg). The ^1H and ^{13}C NMR spectra of the crude oil showed (2*R*)-methyl *N*-acetyl-5-methyl-6-hydroxypipecolate **11** and (2*R*)-methyl *N*-acetyl-4-ethyl-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, CH_3–C5), 1.31–1.79 (m, 5H, H3, 4 5), 2.22 (s, 3H, $COCH_3$), 3.71 (s, 3H, $COOCH_3$), 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, $\mathbf{CH_3}CH_2$), 1.31–1.73 (m, 3H, $CH_3\mathbf{CH_2}$, H4), 2.15 (s, 3H, $COCH_3$), 2.37–2.47 (m, 2H, H3), 3.76 (s, 3H, $COOCH_3$), 4.44–4.53 (m, 1H, H2), 5.29 (m, 1H, H5).

The $CDCl_3$ solutions of **11** and **12** on storing for several hours underwent dehydration to give (2*R*)-methyl *N*-acetyl-5-methyl-5,6-didehydropipecolate **9a** in 30% yield and (2*R*)-*N*-acetyl-4-ethyl-4,5-didehydroprolinate **10a** in 17% yield respectively.

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

Reaction of (2*S*)-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 (2*S*)-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/H_2 (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_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], $COCH_3$), 2.35–2.41 (m, 1H, H4b), 3.73 (s, 3H, [3.75, s], $COOCH_3$), 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). ^{13}C NMR: δ [minor rotamer in brackets] 18.9 [18.6] (C3), 21.5 ($COCH_3$), 23.3 [23.9] (C4), 51.7 [55.7] (C2), 52.3 [52.6] ($COOCH_3$), 107.1 [107.0] (C5), 125.1 [123.2] (C6), 168.5, 171.0 (C1, CONH). Calc. for $C_9H_{13}NO_3$: C, 58.99; H, 7.16; N, 7.65. Found: C, 59.01; H, 7.12; N, 7.60%. $[\alpha]_D^{20}$ −64° (*c* 0.016, CH_3Cl).

(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, CH_3C4), 2.14 (s, 3H, $COCH_3$), 2.50 (m, 1H, H3a), 2.94 (m, 1H, H3b), 3.76 (s, 3H, $COOCH_3$), 4.82 (dd, 1H, $J = 11.7$, 5.1 Hz, H2), 6.22 (q, 1H, $J = 1.8$ Hz, H5). ^{13}C NMR: δ 13.8 ($\mathbf{C}H_3C4$), 21.9 ($COCH_3$), 38.3 (C3), 52.8 ($COOCH_3$), 58.5 (C2), 120.2 (C4), 124.3 (C5), 165.9, 171.9 (C1, CONH). HRMS (ESI^+, MeOH): calc. for $(C_9H_{13}NO_3 + Na)^+$ *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, $COCH_3$), 3.75 (s, 3H, $COOCH_3$), 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). ^{13}C NMR: δ 18.2 (C5), 23.5 ($COCH_3$), 53.0, 54.5 (C2, $COOCH_3$), 125.2, 130.3 (C3, C4), 169.6, 171.8 (C1, CONH). HRMS (ESI^+, MeOH): calc. for $(C_8H_{13}NO_3 + H)^+$ *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. *(2R)-Methyl 2-acetamido-7-formylheptanoate* **14** *and (2R)-methyl 2-acetamido-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/H_2 (400 psi) at 80 °C for 20 h to give a brown oil (80 mg). The ^1H and ^{13}C 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, 1:1) to give a sample of **14** and a sample of **15** containing 20% of the isomer **14**.

The (2*R*)-heptanoate **14** was isolated as a yellow oil (28 mg, 34%), (R_f 0.86). IR (neat): 3296, 2938, 1744, 1657, 1542, 1438, 1438, 1375, 1211, 1167 cm^{-1}. ^{1}H 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], COCH$_3$), 2.41 (td, 2H, J = 7.2, 1.7 Hz, H7), 3.75 (s, 3H, [3.72, s], COOCH$_3$), 4.62 (m, 1H, H2), 6.14 (bs, 1H, NH), 9.73 (t, 1H, J = 1.7 Hz, [9.75, m], CHO). ^{13}C NMR: δ 24.5 (COCH$_3$), 22.1 (C6), 25.3 (C4), 29.0 (C5), 32.6 (C3), 44.0 (C7), 52.3, 52.7 (C2, COOCH$_3$), 170.0, 173.2 (C1, CONH), 202.6 (CHO). HRMS (EI, MeOH): calc. for ($C_{11}H_{19}NO_4$–COCH$_3$) m/z 186.1130, found, 186.1133 (M–COCH$_3$).

The (2*R*)-heptanoate **15** was obtained as a yellow oil (24 mg, 29%), (R_f 0.95) containing 20% of **14**. IR (neat): 1740, 1656, 1545, 1438, 1375, 1212, 1178 cm^{-1}. ^{1}H 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, COCH$_3$), 2.24–2.38 (m, 1H, H6), 3.75 (s, 3H, COOCH$_3$), 4.63 (m, 1H, H2), 6.21 (d, 1H, J = 7.8 Hz, NH), 9.60 (m, 1H, CHO).† ^{13}C 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, COOCH$_3$), 170.1, 173.2 (C1, CONH), 204.9 (CHO). HRMS (EI, MeOH): calc. for ($C_{11}H_{19}NO_4$–COCH$_3$) m/z 186.1130, found, 186.1133 (M–COCH$_3$). 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)$_2$]$_2$:BIPHEPHOS or PPh$_3$ was 100:1:1:2; CO/H$_2$ (1:1 molar mixture).

Reaction of (2*Z*,4*E*)-methyl 2-acetamidohexa-2,4-dienoate 1a. The (2*Z*,4*E*)-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 (2*S*)-pipecolate **9a** was isolated as a clear oil (27 mg, 51%). HPLC showed the ee as 95% (*S*). The (2*S*)-prolinate **10a** was obtained as a clear oil (16 mg, 30%). HPLC showed the ee as 99% (*S*).

Reaction of (2*Z*)-methyl 2-acetamidopenta-2,4-dienoate 1b. A solution of the (2*Z*)-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/H$_2$ and heated to 80 °C for 72 h. After work up, the ^{1}H 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 (2*S*)-pipecolate **9b** was isolated as a clear oil (17 mg, 39%). HPLC showed the ee as 97% (*S*). The (2*S*)-prolinate **10b** was obtained as a colourless oil (9 mg, 21%). HPLC showed the ee as 99% (*S*).

Reaction of (2*Z*)-methyl 2-acetamidohepta-2,6-dienoate 1c. *(2S)-Methyl N-acetyl-6-methyl-6,7-didehydroazepan-1-yl-2-carboxylate* **17** *and (2S)-methyl N-acetyl-5-ethyl-5,6-didehydropipecolate* **18**. The (2*Z*)-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/H$_2$ and heated to 150 °C for 72 h. After work up, the ^{1}H NMR spectrum of the crude oil (40 mg) showed three compounds, (2*S*)-methyl *N*-acetyl-6-methyl-6,7-didehydroazepan-1-yl-2-carboxylate **17**, (2*S*)-methyl *N*-acetyl-5-ethyl-5,6-didehydropipecolate **18** and (2*S*)-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_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-1-yl-2-carboxylate **17**, ^{1}H NMR: δ 1.6–2.2 (m, 6H, H3, H4, H5), 1.74 (d, 3H, J = 1.3 Hz, CH$_3$), 2.09 (s, 3H, COCH$_3$), 3.70 (s, 3H, COOCH$_3$), 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**,^{1}H NMR: δ 1.03 (t, 3H, J = 7.4 Hz, **CH$_3$**CH$_2$), 1.78–1.90 (m, 1H, H3), 1.93–2.09 (m, 4H, H4, CH$_3$**CH$_2$**), 2.23 (s, 3H, COCH$_3$); 2.33–2.40 (m, 1H, H3); 3.71 (s, 3H, COOCH$_3$); 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}. ^{1}H 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, COCH$_3$), 3.75 (s, 3H, COOCH$_3$), 4.61 (m, 1H, H2), 6.19 (bd, 1H, J 7.2 Hz, NH). ^{13}C NMR: δ 14.3 (C7), 22.8 (C4), 23.6 (COCH$_3$), 25.2 (C5), 31.7, 32.9 (C3, C6), 52.5, 52.7, C2, COOCH$_3$), 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 (2*Z*,4*E*)-methyl 2-acetamidohexa-2,4-dienoate 1a. The (2*Z*,4*E*)-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/H$_2$ and heated to 150 °C for 72 h. After work up, the ^{1}H NMR spectrum of the crude oil (40 mg) showed only the pipecolate **9a**. Purification using chromatography (ethyl acetate:light petroleum = 3:1) gave the (2*S*)-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** (^{1}H NMR: δ 9.76).

Reaction of (2*Z*)-methyl 2-acetamidopenta-2,4-dienoate 1b. The (2*Z*)-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/H$_2$ 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 ^{1}H 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 (2*S*)-pipecolate **9b** was isolated as a clear oil (22 mg, 40%). HPLC showed the ee as 94% (*S*). The (2*S*)-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 (2*Z*)-methyl 2-acetamidohepta-2,6-dienoate 1c. The (2*Z*)-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/H_2 and heated to 150 °C for 72 h. After work up, the ^{1}H NMR spectrum of the crude oil (40 mg) showed the (2*S*)-methyl *N*-acetyl-5-ethyl-5,6-didehydropipecolate **18** and (2*S*)-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_f 0.35). IR (neat) 3339, 2953, 1744, 1656, 1406, 1378, 1311, 1205, 1172, 1033 cm^{-1}. ^{1}H NMR: δ 1.03 (t, 3H, $J = 7.4$ Hz, $\mathbf{CH_3}CH_2$), 1.78–1.90 (m, 1H, H3), 1.93–2.09 (m, 4H, H4, $CH_3\mathbf{CH_2}$), 2.23 (s, 3H, $COCH_3$); 2.33–2.40 (m, 1H, H3); 3.71 (s, 3H, $COOCH_3$); 5.20 (m, 1H, H2); 6.39 (bs, 1H, H6). ^{13}C NMR: δ 12.7 ($\mathbf{CH_3}CH_2$), 21.6 ($CO\mathbf{C}H_3$), 22.6 (C4), 23.7 (C3), 28.4 ($CH_3\mathbf{C}H_2$), 51.7 (C2), 52.6 ($COO\mathbf{C}H_3$), 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

(2*R*)-Methyl *N*-acetylpipecolate 20. (2*R*)-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%). ^{1}H 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]). ^{13}C NMR: δ [minor rotamer in brackets] 21.0 [20.9], 21.8 [21.6] ($CO\mathbf{C}H_3$), 25.4 [24.6], 26.7 [27.4], 44.3 [39.3] (C6), 51.8 [52.6] ($COO\mathbf{C}H_3$), 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 $(M + Na)^+$.

(2*R*)-Pipecolinic acid hydrochloride 21. (2*R*)-Methyl *N*-acetylpipecolate **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 ^{1}H and ^{13}C NMR spectra in D_2O were consistent with literature data.[33] ^{1}H NMR: δ (CD_3OD) 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° (c 0.002, H_2O) (lit.[26] for (2R)-**21**, $[\alpha]_D^{20}$ +10.8° (c 2, H_2O)).

Acknowledgements

We thank Monash University and the Centre for Green Chemistry for provision of a postgraduate award (to E. T.), the Australian Research Council for its financial support to research and Johnson Matthey Pty Ltd for a loan of rhodium.

References

1 R. A. Sheldon, *Chem. Ind.*, 1997, 12.
2 A. Bruggink, *Chim. Oggi*, 1998, **16**, 44.
3 B. M. Trost, *Angew. Chem.*, 1995, **107**, 285; B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 259.
4 E. J. Corey and X.-M. Cheng, *The Logic of Chemical Synthesis*, Wiley, New York, 1989, ch. 4, p. 47–57.
5 E. Teoh, E. M. Campi, W. R. Jackson and A. J. Robinson, *J. Chem. Soc., Chem. Commun.*, 2002, 978.
6 H. Takahara, H. Bandoh and T. Momose, *Tetrahedron*, 1993, **49**, 11 205.
7 A. F. Parsons, *Tetrahedron*, 1996, **52**, 4149.
8 S. Hanessian, G. McNaughton-Smith, H.-G. Lombart and W. D. Lubell, *Tetrahedron*, 1997, **53**, 12 789.
9 B. Breit and S. K. Zahn, *Angew. Chem., Int. Ed.*, 2001, **40**, 1910.
10 B. Breit and S. K. Zahn, *Angew. Chem., Int. Ed.*, 1999, **38**, 969.
11 M. Beller, B. Zimmermann and H. Geissler, *Chem. Eur. J.*, 1999, **5**, 1301.
12 B. Breit, *Chem. Eur. J.*, 2000, **6**, 1519.
13 R. I. Pugh, E. Drent and P. G. Pringle, *J. Chem. Soc., Chem. Commun.*, 2001, 1476.
14 M. J. Burk, J. G. Allen and W. F. Kiesman, *J. Am. Chem. Soc.*, 1998, **120**, 657.
15 U. Schmidt, A. Lieberknecht and J. Wild, *Synthesis*, 1984, 53.
16 U. Zoller and D. Ben-Ishai, *Tetrahedron*, 1975, **31**, 863.
17 R. M. Williams, D. J. Aldous and S. C. Aldous, *J. Org. Chem.*, 1990, **55**, 4657.
18 A. Maercker, *Org. React.*, 1965, **14**, 335.
19 M. J. Burk, J. E. Feaster, W. A. Nugent and R. L. Harlow, *J. Am. Chem. Soc.*, 1993, **115**, 10 125.
20 I. Ojima and Z. Zhang, *J. Organomet. Chem.*, 1991, **417**, 253.
21 D. Anastasiou and W. R. Jackson, *J. Organomet. Chem.*, 1991, **413**, 399; D. J. Bergmann, E. M. Campi, W. R. Jackson, Q. J. McCubbin and A. F. Patti, *Tetrahedron*, 1997, **53**, 17 449; D. J. Bergmann, E. M. Campi, W. R. Jackson and A. F. Patti, *Aust. J. Chem.*, 1999, **52**, 1131.
22 I. Ojima, M. Tzamarioudaki and M. Eguchi, *J. Org. Chem.*, 1995, **60**, 7078.
23 E. Billig, A. G. Abatjoglou and D. R. Bryant, U.S. Patents 4,668,651 (1987) and 4,769.498 (1998); G. D. Cuny and S. L. Buchwald, *J. Am. Chem. Soc.*, 1993, **115**, 2066.
24 H. Klein, R. Jackstell, K.-D. Wiese, C. Borgmann and M. Beller, *Angew. Chem., Int. Ed.*, 2001, **40**, 3408.
25 A. J. Robinson, C.-Y. Lim, L. He, P. Ma and M.-Y. Li, *J. Org. Chem.*, 2001, **66**, 4141.
26 U. Schiedt and H. G. Höss, *Z. Physiol. Chem.*, 1957, **308**, 179.
27 A. J. Robinson, P. Stanislawski, D. Mulholland, L. He and H.-Y. Li, *J. Org. Chem.*, 2001, **66**, 4148.
28 J. Mancuso, D. Swern and S. L. Huang, *J. Org. Chem.*, 1978, **43**, 2480.
29 J. Mancuso and D. Swern, *Synthesis*, 1981, 165.
30 M. Whittaker, C. R. McArthur and C. C. Leznoff, *Can. J. Chem.*, 1985, **63**, 2844.
31 T. Ventrice, E. M. Campi, W. R. Jackson and A. F. Patti, *Tetrahedron*, 2001, **57**, 7557.
32 J. Toone and J. B. Jones, *Can. J. Chem.*, 1987, **65**, 2722.
33 D. C. R. Hockless, R. C. Mayadunne and S. B. Wild, *Tetrahedron: Asymmetry*, 1995, **6**, 3031; S. Nazabadioko, R. J. Pérez, R. Brieva and V. Gotor, *Tetrahedron: Asymmetry*, 1998, **9**, 1597.