A new enantioselective synthesis of β-amino acids

Dilek Saylik, a Eva M. Campi, a Andrew C. Donohue, a W. Roy Jackson a,b,* and Andrea J. Robinson a

a School of Chemistry, PO Box 23, Monash University, Victoria 3800, Australia
b Centre for Green Chemistry, PO Box 23, Monash University, Victoria 3800, Australia

Received 5 February 2001; accepted 26 February 2001

Abstract—Enantioselective hydrogenation of some α,β-unsaturated nitriles and their corresponding methyl esters bearing a phthalimidomethyl substituent at the α-carbon using Rh-DuPHOS catalysts afforded β-amino acid precursors with modest e.e.s of up to 48%. Hydrogenation of the α,β-unsaturated methyl esters using a Ru-BINAP catalyst gave higher e.e.s of up to 84%. Method development for the determination of the enantiomeric excesses of these derivatives using chiral HPLC is also reported. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Unsaturated nitriles bearing an α-phthalimidomethyl substituent 1 can be prepared by the nickel-catalysed addition of hydrogen cyanide (CAUTION)† to appropriate alkynes 2 and hydrogenated over Pd/CaCO 3 to give β-amino acid precursors 3† (Scheme 1).

In this paper, attempts to carry out enantioselective conversions of 1 to 3 are described. The importance of amide substituents in promoting enantioselectivity in double bond hydrogenations using both Rh and Ru catalysts has been established and extensively discussed.2–4 It has been established that enantioselective Rh-catalysed reactions of α-N-acylacrylates are facilitated by secondary binding of the amide carbonyl group with Rh in the alkyl–Rh(III) intermediate through a five-membered chelate 4 (Fig. 1).5 It appeared to us that the phthalimido derivatives 1 could possibly also stabilise Rh(III) intermediates through the formation of a six-membered chelate 5. Similar six-ring chelates could be formed via N-acetyl or N-Boc-

Scheme 1. R = a, H; b, Me; c, Ph; d, TBDMS; e, TMS; L* = (R,R)-Et-DuPHOS or (R,R)-Me-BPE.

† Corresponding author. Tel.: +61-03-9905-4552; fax: +61-03-9905-4597; e-mail: w.r.jackson@sci.monash.edu.au
† Use of HCN is hazardous and suitable precautions for use and disposal must be taken.

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PH: S0957-4166(01)00097-0
2. Results and discussion

2.1. Preparation of substrates

Substrates 1 were prepared by Ni[P(OPh)₃]₄-catalysed addition of hydrogen cyanide to the alkynes 2. Compounds 1a–1e have been prepared previously and similar yields of 1 together with similar percentages of the undesired isomers 6 were obtained.¹ Hydrocyanation of the TBDMS and the TMS analogues 2d and 2e gave the desired isomers 1d and 1e together with 6d and 6e in ratios of 85:15 and 73:27, respectively. The N-acetyl 7 and N-Boc 8 analogues (Fig. 2) of the phthalimido nitriles 1a were prepared by similar hydrocyanation of the N-acetyl and N-Boc 3-amino-1-propynes.

Methanolysis of the phthalimido nitriles 1a and 1b gave the corresponding methyl esters 9a and 9b (Scheme 2). Several attempts to prepare N-acyl derivatives of the unsaturated amino acid 10a were unsuccessful and led to uncharacterisable insoluble products.

2.2. Hydrogenations of phthalimido nitriles

The phthalimido nitriles 1a–1e were hydrogenated using (R,R)-Et-DuPHOS-Rh(I) and (R,R)-Me-BPE-Rh(I) (Scheme 1) and the results are summarised in Table 1. Reactions of the methylene compound 1a using the DuPHOS-Rh catalyst gave high yields of the saturated compound 3a when MeOH or MeCN were used as solvent but no reaction occurred in THF at ambient temperature and 70 psi H₂ (entries 1–3). Similarly, a high yield was obtained when the BPE-Rh catalyst was used in MeOH (entry 4).

The specific rotation of the product 3a from the (R,R)-DuPHOS-Rh catalysed reaction in MeOH (+8.3) was significantly higher than the value obtained from the same reaction in MeCN (cf. entries 1 and 2). Hydrogenation using the (R,R)-BPE-Rh system in MeCN gave a similar e.e. (by HPLC). The specific rotation was lower and also of opposite sign to the product obtained from reactions using the (R,R)-DuPHOS-Rh catalyst.

Scheme 2. R = a, H; b, Me.
A sample of the product $3a$ with $[\alpha]_D +8.3$ was hydrolysed using conc. HCl to give a sample of the hydrochloride salt of $\alpha$-methyl-$\beta$-alanine $11$ which was converted to the free amino acid $12$ by passing through an Amberlite column (Scheme 3).

The specific rotation of the free amino acid $12$, $[\alpha]_D +19$ was at the higher end of the range of values reported in the literature, where $[\alpha]_D$ values of $-14$ and $-21^9,10$ have been recorded under identical conditions, i.e. $c=0.42$ in $H_2O$, for the $(R)$-enantiomer. Preferential formation of the $(S)$-enantiomer using a $(R,R)$-Et-DuPHOS-Rh catalyst is also opposite to that shown for hydrogenations of $\alpha$-$N$-acylacrylates where the $(R,R)$-catalyst leads to a preference for $(R)$-configured $\alpha$-amino acids. $^7c$ Surprisingly, the $(R,R)$-Me-BPE-Rh system led to a preference for the opposite $(R)$-enantiomer. It should be noted that small changes in the substitution pattern of the phosphine ligand, for example from Me, Et and $n$-Pr to $i$-Pr in the case of DuPHOS, can lead to a change in the absolute configuration of the product. $^7c$

The inconsistencies in using the specific rotation values of free amino acids as measures of enantioselectivity are well known$^{11}$ and thus the amino acid was converted into its Fmoc-derivative $13$ (Scheme 3). The sample was then compared with an authentic sample of the $(S)$-Fmoc derivative prepared by Seebach et al. $^{12}$ Unfortunately, the sample prepared by us showed variable solubility and $[\alpha]_D$ values in contrast to the material prepared by Seebach. An alternative method for determining the reaction enantioselectivity was therefore sought. The amino acid $12$ was converted into the $N$-benzoyl ethyl ester $14$ (Scheme 3), which was successfully resolved by chiral HPLC using a Chiralcel OJ column. The enantioselectivity was shown to be a dis-

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**Table 1.** Enantioselective hydrogenation of $\alpha,\beta$-unsaturated phthalimido nitriles $1$ using Rh catalysts$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate 1, $R =$</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Pressure (psi)</th>
<th>$[\alpha]_D$</th>
<th>e.e.$^b$ (%)</th>
<th>Product yield (%)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$1a$, H</td>
<td>DuPHOS-Rh$^d$</td>
<td>MeOH</td>
<td>20</td>
<td>70</td>
<td>+8.3</td>
<td>14</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>$1a$, H</td>
<td>DuPHOS-Rh</td>
<td>MeCN</td>
<td>20</td>
<td>70</td>
<td>+1.0</td>
<td>4</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>$1a$, H</td>
<td>DuPHOS-Rh</td>
<td>THF</td>
<td>20</td>
<td>70</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>$1a$, H</td>
<td>BPE-Rh$^e$</td>
<td>MeOH</td>
<td>20</td>
<td>60</td>
<td>–6.8</td>
<td>12</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>$1b$, Me</td>
<td>DuPHOS-Rh</td>
<td>MeOH</td>
<td>40</td>
<td>100</td>
<td>+1.0</td>
<td>33</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>$1c$, Ph</td>
<td>DuPHOS-Rh</td>
<td>MeOH</td>
<td>40</td>
<td>100</td>
<td>0.0</td>
<td>3</td>
<td>78</td>
</tr>
<tr>
<td>7</td>
<td>$1d$, TBDMS</td>
<td>DuPHOS-Rh</td>
<td>$C_6H_6$</td>
<td>40</td>
<td>100</td>
<td>–8.3</td>
<td>48</td>
<td>84</td>
</tr>
<tr>
<td>8</td>
<td>$1e$, TMS</td>
<td>DuPHOS-Rh</td>
<td>MeOH</td>
<td>40</td>
<td>100</td>
<td>+2.5</td>
<td>14</td>
<td>93</td>
</tr>
</tbody>
</table>

$^a$ Reductions for 24 h.

$^b$ Enantiomeric excess determined by HPLC (see below).

$^c$ Isolated yield after chromatography.

$^d$ $(R,R)$-Et-DuPHOS-Rh(I).

$^e$ $(R,R)$-Me-BPE-Rh(I).
The possibility that these hydrogenations involved an initial isomerisation of 1 merited investigation since the resultant \( \alpha,\beta \)-unsaturated amide 15 (Scheme 4) would also be expected to hydrogenate smoothly in line with the many literature examples.\(^2\) Reactions of the nitriles 1a and 1b with deuterium using \((R,R)\)-Et-DuPHOS-Rh(I) gave no evidence for deuterium incorporation into the CH\(_2\) adjacent to the phthalimido group (Scheme 4). The \( ^1\)H, \( ^2\)H and \( ^{13}\)C NMR spectra of the products were consistent with deuterium incorporation as shown in the phthalimido nitrile 16.

### 2.3. Hydrogenations of phthalimido esters

The phthalimido nitriles 1 were converted into the phthalimido methyl esters 9 which were hydrogenated using the BINAP-Ru and DuPHOS-Rh catalysts (Scheme 5). Excellent enantioselectivities have been reported for enantioselective hydrogenations of \( \alpha,\beta \)-unsaturated esters with \( \alpha,\beta \)-amido\(^8,14\) substituents or an \( \alpha\)-CH\(_2\)CO\(_2\)Me substituent.\(^15\)

Hydrogenation of 9a using BINAP-Ru at ambient temperature with a H\(_2\) pressure of either 100 or 50 psi gave excellent yields of the phthalimido ester 17a with good enantioselectivity, 80 and 84\% e.e., respectively (entries 9 and 10, Table 2). A hydrogenation using the DuPHOS-Rh catalyst gave a low e.e., 12\% (entry 11), similar to that obtained in the hydrogenation of the phthalimido nitrile 1a using this catalyst (entry 1, Table 1). Disappointingly, reaction of the homologue 9b also gave poor enantioselectivity, with an e.e. of 10\% (entry 12, Table 2), using the BINAP-Ru catalyst.

Hydrolysis of the phthalimido ester 17a gave \( \alpha\)-methyl-\( \beta \)-alanine 12 with \([\alpha]_D\) \(-8.2\) (c 0.31, H\(_2\)O), again within the range of values previously reported.\(^9,11\) The \( \alpha\)-methyl-\( \beta \)-alanine obtained using (S)-BINAP-Ru had (R)-absolute configuration, opposite to that obtained using \((R,R)\)-Et-DuPHOS-Rh, which was consistent with related hydrogenations of acetamido acrylates.\(^16\) The saturated ester obtained using \((R,R)\)-Et-DuPHOS-Rh showed a small positive rotation, consistent with a preference for formation of the (S)-enantiomer of 17a.

### 2.4. Hydrogenations of NHAc and NHBoc nitriles

Hydrogenation of the acetamido nitrile 7 using \((R,R)\)-Et-DuPHOS-Rh(I) gave the saturated compound 18 in high yield (89\%) (Fig. 3). The e.e. was shown to be 64\%
by HPLC using a Chiralcel OB column and the product was shown to have an excess of the (S)-enantiomer by hydrolysis to a sample of \( \alpha \)-methyl-\( \beta \)-alanine 12 with an 
[\( \beta \)]\( _{D} \) +7.6. In contrast, hydrogenation of the NHBoc derivative 8 using similar conditions gave only racemic product 19 (Fig. 3).

3. Conclusion

Enantioselective hydrogenation of acyl derivatives of \( \alpha \)-aminomethyl substituted \( \alpha \),\( \beta \)-unsaturated nitriles and esters give \( \beta \)-amino acid precursors in good yield and with e.e. values ranging from 0% to 84%. The highest e.e.s were obtained in the hydrogenation of the phthalimido ester 9a with the BINAP-Ru catalyst. Introduction of a \( \beta \)-substituent, as in 9b, led to a significant decrease in e.e. In contrast, the highest e.e.s from hydrogenation of the phthalimido nitriles 1 were obtained from \( \beta \)-Me or \( \beta \)-TBDMS substituted compounds with DuPHOS-Rh as catalyst, substantiating the theory that this enantioselective hydrogenation is substrate specific.

HPLC conditions were established for determination of the enantiomeric excess of these \( \beta \)-amino acid precursors.

4. Experimental

4.1. General

Melting points were determined using a Gallenkamp MFB-595 melting point apparatus and are uncorrected. Microanalyses were performed either by Chemical and Micro Analytical Services Pty Ltd, Melbourne or by the University of Otago, Chemistry Department, Dunedin, New Zealand. NMR spectra were recorded on a Bruker AC-200 spectrometer operating at 200 (\( ^{1} \)H) and 50 (\( ^{13} \)C) MHz, on a Bruker DPX-300 spectrometer operating at 300 (\( ^{1} \)H) and 75 (\( ^{13} \)C) MHz, or on a Bruker DRX-400 spectrometer operating at 400 (\( ^{1} \)H), 100 (\( ^{13} \)C) and 61.4 (\( ^{1} \)H) MHz using either Me\( _{4} \)Si (\( ^{1} \)H) or the solvent peak (\( ^{13} \)C, \( ^{1} \)H) as the reference. Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrophotometer. Low resolution electron impact mass spectra (EI) were obtained on a Fisons TR10-1000 mass spectrometer. Accurate mass measurements were obtained at high resolution with a Bruker BioApex 47e FTMS and a 4.7 T superconducting magnet. The instrument was externally calibrated with FC5311. Flash column chromatography was carried out using 40–63 \( \mu \)m (230–400 mesh) silica gel 60 (Merck no. 9385). Analytical thin-layer chromatography (TLC) was performed on Polygram Sil G/UV\( _{254} \) plates. Optical rotations were measured with a Perkin-Elmer 141 polarimeter (in a cell length of 1 dm) at a wavelength of 589 nm (sodium D line) at a temperature of 20°C. High-performance liquid chromatography (HPLC) was performed on two instruments. One system involved a Waters Model 6000A (Column: Deltapak C18—100 A, 3.9 mm\( \times \)30 cm, 10 \( \mu \)L), Waters gradient programme model 660 and Waters model 481 detector. Product distributions were obtained from peak areas from a peak printout using HP Chemstation 3365 Series II software. Alternatively, HPLC was performed on a Varian LC model 5000 with a Varian UV-50 detector. Product distributions were obtained from peak areas in a peak printout using Class LC 10 software. The columns used were Chiralcel OB (column no. OB00CE-1H013), Chiralcel OD (column no. OD00CE-HL011) and Chiralcel OJ (column no. OJ00CE-JJ028). Both the Chiralcel OB and OJ columns have a cellulose ester derivative coated on silica gel adsorbent while the Chiralcel OD has a cellulose carbamate derivative on silica gel adsorbent. All columns were 0.46 cm ID\( \times \)25 cm with a particle size of 10 \( \mu \)m. Retention times (\( t_{R} \)) are an average of two runs.

Solvents were purified according to standard procedures. Chloroform used for optical rotations was of analytical purity. (\( \sim \))1.2-Bis(2R,5R)-2,5-diethylphospholano]benzene(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate [(R,R)-EtDuPHOS-Rh(I)] and (R,R)-\( \sim \) - 1.2 bis(\( \sim \)-methoxyphenyl)(phenyl)phosphino]ethane(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate [(R,R)-MeBPE-Rh(I)] were used as supplied from Strem Chemicals. [(S)-\( \sim \) -2,2'-(Bis(diphenylphosphino)-1,1'-binaphthyl]chloro[p-cymene]ruthenium chloride [(S)-BINAP-Ru(II)] was used as supplied from Fluka. Palladium on calcium carbonate (5%, Pd/ CaCO\( _{3} \)) was obtained from Aldrich. Starting materials and reagents were purchased from Sigma–Aldrich and were used without further purification. Nitrogen and hydrogen (supplied by BOC Gases) and deuterium (99.5%) (supplied by CIG Gases) gases, used in the hydrogenation reactions to purge and fill the system, were of high purity (<10 ppm oxygen) and additional purification was achieved by passage of the gases through water, oxygen and hydrocarbon traps. Solvents used for metal-catalysed reactions were degassed by bubbling high purity nitrogen through for 60 min prior to use.

4.2. Preparation of alkynes

The phthalimido alkynes 2a–2c, \( \sim \)-prop-2-ynyl)-acetamide and terr-butyl \( \sim \)-prop-2-ynyl)carbamate were prepared as described in the literature.\( ^{19} \)

4.2.1. \( \sim \)-[\( \sim \)-Butyldimethylsilyl]prop - \( \sim \)-ynyl]phtthalimide 2d. Compound 2d was prepared from the corresponding alcohol as described by Landini\( ^{17} \) and recrystallised from ethanol as colourless crystals (yield:
4.3.1. General procedure for hydrocyanation reactions

All hydrocyanation reactions were carried out in a 75 mL stainless steel autoclave as described previously. The substrate (5 mmol), catalyst (Ni[P(OH)₃]₄ (1000 μmol), ligand (P(OH)₃ (1 mmol)) and dry degassed benzene (10 mL) were placed in order, in the autoclave under a nitrogen atmosphere. Hydrogen cyanide (5 mmol) was added using a gas-tight syringe. In some cases, when ambient temperature exceeded 20°C, a larger volume of HCN was used. The reactor was sealed and heated at 120°C for the required time. The autoclave was cooled, the excess hydrogen cyanide was vented and the benzene removed. The catalyst was precipitated with chloroform and removed by filtration and the solvent removed to vacuo to give the crude product. Flash chromatography (silica, ethyl acetate/light petroleum) gave the product nitriles.

4.3.2. 2-(2-Cyanoprop-2-enyl)phthalimide 1a

Obtained from 2a as a mixture with (E)-2-(3-cyanoprop-2-enyl)phthalimide 6a in the ratio 85:15, respectively, as a white solid. Yield: 68%; mp 71–72°C; ¹³C NMR (100 MHz, CDCl₃) δ 39.6 (C-1'), 116.6 (C-2'), 180.0 (CN), 123.8 (C-4'), 131.7 (C-3'), 132.9 (C-3'a/7a), 134.5 (C-5/6'), 167.1 (CO). ¹H NMR spectral data were consistent with the literature.¹³

4.3.3. (E)-2-(2-Cyano-3-phenylprop-2-enyl)phthalimide 1e

Yield: 58%; ¹³C NMR (100 MHz, CDCl₃) δ 36.1 (C-1'), 111.1 (C-2'), 117.9 (CN), 123.7 (C-4'), 128.9, 129.4, 130.0 (ArCH), 131.8 (C-3'a/7a), 133.1 (ArC), 134.3 (C-5/6'), 146.5 (C-3'), 167.3 (CO).

4.3.4. (E)-2-[3-(3-Butylmethyisilyl)-2-cyanoprop-2-enyl]phthalimide 1d

Yield: 75%; mp 125–128°C; IR: ν = 2923, 2854, 2206, 1771, 1722, 1463, 1378, 1341, 1309, 1252, 950, 826, 711 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.32 (s, 6H, Si(CH₃)₃), 0.98 (s, 9H, (CH₃)₃C), 4.52 (2H, J = 1.6 Hz, 1H-CH), 6.81 (t, 1H, J = 1.5 Hz, 3'-CH), 7.75 (m, 2H, ArH), 7.88 (m, 2H, ArH); ¹³C NMR (75 MHz, CDCl₃) δ 49.4 (Si(CH₃)₃), 17.1 ((CH₃)₃C), 26.2 ((CH₃)₃C), 39.2 (C-1'), 117.5 (CN), 123.4 (C-4'), 125.2 (C-2'), 131.8 (C-3'a/7a), 134.3 (C-5/6'), 150.8 (C-3'), 167.3 (CO) (MS (EI): m/z 326 (M⁺, 1%), 311 (3), 270 (19), 269 (100), 242 (4), 130 (70), 102 (27), 75 (27), 57 (23); C₇H₈NO₃Si (323.45) calecd: C, 66.2; H, 6.8; N, 8.6; found: C, 66.6; H, 7.1; N, 8.5%.

4.3.5. (E)-2-[2-Cyanocyp-3-(trimethylsilyl)prop-2-enyl]phthalimide 1e

Yield: 70%; mp 82–84.5°C; IR: v = 2925, 2854, 2211, 1771, 1719, 1465, 1430, 1390, 1343, 1253, 1190, 1122, 948, 865, 848, 737, 711 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.32 (s, 9H, (CH₃)₃C), 4.50 (2H, J = 1.4 Hz, 1H-CH), 6.77 (t, J = 1.3 Hz, 1H, 3'-CH), 7.74 (m, 2H, ArH), 7.86 (m, 2H, ArH); ¹³C NMR (75 MHz, CDCl₃) δ 0.70 (Si(CH₃)₃), 39.1 (C-1'), 117.5 (CN), 123.7 (C-4'), 123.8 (C-2'), 131.8 (C-3'a/7a), 134.3 (C-5/6'), 151.3 (C-3'), 167.3 (CO) (MS (EI): m/z 284 (M⁺, 3%), 283 (4), 270 (18), 269 (76), 205 (18), 204 (82), 160 (35), 130 (100), 105 (10), 104 (16), 102 (47), 77 (30), 73 (40), 58 (14); C₁₁H₁₀N₂O₃Si (284.39) calecd: C, 63.4; H, 5.7; N, 9.8; found: C, 63.4; H, 5.7; N, 9.5%.

4.3.6. N-(2-Cyanoprop-2-enyl)acetamide 7

Distillation of the hexane insoluble fraction gave compound 7 as a colourless oil (yield: 29%); bp (oven) 150°C/0.2 mm; IR: v = 3320, 3076, 2936, 2267, 1662, 1548, 1428, 1374, 1289, 1033, 953 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.04 (s, 3H, CH₃), 4.01 (dt, 2H, J = 6.2, 1.3 Hz, 1H-CH), 5.95 (t, 1H, J = 1.5 Hz, 3'-CH(E)), 5.99 (t, 1H, J = 1.2 Hz, 3'-CH(Z)), 6.46 (bs, 1H, NH); ¹³C NMR (100 MHz, CDCl₃) δ 22.9 (CH₃), 41.8 (C-1'), 117.3 (CN), 120.2 (C-2'), 131.6 (C-3'), 170.5 (CO) (MS (EI): m/z 124 (M⁺, 12%), 109 (8), 82 (100), 81 (57), 66 (42), 55 (30), 54 (40), 52 (43), 51 (36); HRMS (EI): m/z calecd for C₆H₈N₂O: 124.0637; found: 124.0636.

4.3.7. t-Butyl N-(2-cyano-2-propenyl)carbamate 8

Compound 8 was isolated by chromatography (ethyl acetate/light petroleum:ammonia solution, 2:8:1) as a colourless oil (yield: 42%); bp (oven) 140°C/0.12 mm; IR: v = 3350, 2979, 2930, 2227, 1699, 1516, 1368, 1252, 1170, 1053, 949, 862 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 1.46 (s, 9H, (CH₃)₃C), 3.89 (bd, 2H, J = 0.6 Hz, 1H-CH), 4.90 (bs, 1H, NH), 5.92 (bt, 1H, J = 1.5 Hz, 3'-CH(E)), 5.89 (t, 1H, J = 1.3 Hz, 3'-CH(Z)); ¹³C NMR (75 MHz, CDCl₃) δ 28.3 ((CH₃)₃C), 43.1 (C-1'), 80.4 ((CH₃)₃C), 117.3 (CN), 121.0 (C-2'), 130.7 (C-3'), 155.3 (CO) (MS (EI): m/z 167 (M⁺-CH₃, 9%), 149 (12),
127 (80), 126 (100), 123 (20), 109 (26); C6H14N2O2
(182.22) caked: C, 59.32; H, 7.74; N, 15.37; found: C,
59.27; H, 7.68; N, 15.36%.

4.4. 2-(Phthalimidomethyl)alkenoates 9

Concentrated sulfuric acid (11.0 g, 112.2 mmol) was
added slowly with frequent shaking to an ice-cold
solution of the cyanophthalimide 1a or 1b (1.37 mmol) in
methanol (12.0 g).

4.4.1. Methyl 2-(phthalimidomethyl)prop-2-enoate 9a

White solid, mp 93–96°C; yield: 54%; IR: v = 3056, 2988,
2954, 1774, 1730, 1046, 1439, 1438, 1397, 1363, 1332, 1202,
1145, 1058 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.05 (d,
3H, CH₃), 4.58 (s, 2H, NCH₂), 5.59 (t, 1H, J = 1.5 Hz, 3-CH(E)),
6.32 (t, 1H, J = 1.1 Hz, 3-CH(Z)), 7.74 (m, 2H, ArH), 7.87 (m,
2H, ArH); ¹³C NMR (75 MHz, CDCl₃) δ 134.1 (C-5', 6'),
134.5 (C-2), 165.7, 167.7 (CO); MS (EI): m/z 214 (M¹⁻CH₃, 37%),
213 (100), 186 (22), 185 (64), 160 (28), 157 (19), 130 (17),
104 (25), 77 (13), 76 (23), 44 (16); C₁₀H₁₄N₂O₂ (226.26) caked:
C, 56.73; H, 7.13; N, 15.36%.

4.4.2. (E)-Methyl 2-(phthalimidomethyl)but-2-enoate 9b

Compound 9b was obtained as a pale yellow oil that
solidified on standing, mp 80–83°C; yield: 41%; IR: v = 3056,
2988, 2954, 1774, 1720, 1469, 1438, 1397, 1363, 1332, 1202,
1145, 1058 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 2.05 (d,
3H, CH₃), 4.58 (s, 2H, NCH₂), 4.56 (t, 2H, J = 1.5 Hz, NCH₂),
5.59 (t, 1H, J = 1.5 Hz, 3-CH(E)), 5.59 (t, 1H, J = 1.1 Hz,
3-CH(Z)), 7.69 (m, 2H, ArH), 7.82 (m, 2H, ArH); ¹³C NMR
(75 MHz, CDCl₃) δ 133.8 (C-5', 6'), 134.3 (C-2), 166.8, 167.8 (CO);
C₁₀H₁₄N₂O₂ (226.26) caked: C, 56.73; H, 7.13; N, 15.36%;
found: C, 64.84; H, 5.05; N, 5.40; d, 5.26%.

4.5. 2-(Aminomethyl)prop-2-enoic acid hydrochloride
10a

2-(Aminomethyl)prop-2-enoic acid hydrochloride 10a
was prepared as described in the literature. The ¹H
NMR spectral data were consistent with that previously
reported.

4.6. Hydrogenation reactions

Method 1: Reactions employing Pd/CaCO₃ were
performed in a 100 mL stainless steel Parr autoclave,
lined with a glass sleeve, equipped with a magnetic Teflon-
coated stirrer bead and heated in a thermostat con-
trolled Eurotherm heating block. The reactor was
charged with the catalyst (10–50 mg), substrate (30–160
mg) and dry, degassed solvent (4–10 mL). The vessel
was evacuated and flushed with hydrogen gas three
times before the autoclave was filled with hydrogen gas
to a pressure that exceeded the desired reaction pres-
sure. The autoclave was tested for leaks and the mixture
filtered through a Celite pad and the solvent removed
in vacuo. The crude product was purified by flash chro-
matography (silica, ethyl acetate/light petroleum, 20:80
unless otherwise noted).

Method 2: Reactions involving the asymmetric homoge-
neous catalysts (Rh and Ru complexes of DuPHOS,
BPE and BINAP) were performed using a drybox. In
the drybox, a Fisher–Porter shielded aerosol pressure
reactor was charged with catalyst (1–2 mg), substrate
(60–250 mg) and dry, deoxygenated solvent (ca. 5 mL).
The reaction vessel was assembled and tightly sealed
within the drybox. The apparatus was connected to the
manifold and the line was purged three times using a
vacuum and nitrogen flushing cycle before the pressure
vessel was opened to the manifold and purged three
times using a vacuum and hydrogen flushing cycle. The
reactor was filled with hydrogen to a pressure of 70 psi
unless otherwise stated and the reaction was stirred at
ambient temperature (20°C or 40°C) for 24 h unless noted
otherwise. The hydrogen gas was vented and the contents
were transferred to a flask and the solvent removed in
vacuo. Purification was achieved by flash chromatogra-
phy as described above.

Hydrogenation experiments are described in the follow-
ing format: substrate, solvent, catalyst, hydrogen pres-
sure, reaction temperature, reaction time, isolated yield,
retention time (HPLC conditions), enantiomeric excess
assigned configuration) and optical rotation.

The assigned configuration of amino acid derivatives
of z-methyl-β-alanine is based on the configuration of the
hydrolysed amino acid compared with the absolute
configuration of z-methyl-β-alanine 12. Retention time
(tᵣ) is quoted for the major enantiomer.

4.6.1. 2-(2-Cyanopropyl)phthalimide 3a. (a) 2-(2'-
Cyanopropyl)prop-2'-enylphthalalimide 1a (30.5 mg), ethyl
acetate (4 mL), Pd/CaCO₃ (10.0 mg) using Method 1
gave 3a, yield 95%, HPLC: tᵣ = 36 and 43 min (Chiralcel
OB, flow rate = 1 mL/min, detection at 254 nm,
elucent = 90% hexane:10% 2-propanol. (b) A mixture of
2-(2'-cyanopropenyl-2'-eny)phthalimide 1a (and
(E)-2-(2'-cyanoprop-2'-eny)phthalalimide 6a (isomer ratio 85:15)
(930 mg), methanol (15 mL), (R,R)-EtDuPHOS-Rh-III
t (10 mg), 70 psi H₂ using Method 2 gave 3a, yield 86% (and
6a, yield 13%), HPLC (for 3a): tᵣ = 36 min, 14% e.e. (S), [α]D +8.3 (c 2.0, CHCl₃), (c) Nitriles 1a and 6a (ratio 85:15) (101 mg), acetonitrile (5 mL), (R,R)-
EtDuPHOS-Rh(II) (1 mg), 70 psi H₂ using Method 2,
gave 3a, yield 81% (and 6a, yield 12%), HPLC (for 3a):
the catalyst (10–50 mg), substrate (30–160 mg) was prepared as described in the literature. The ¹H NMR spectral data were consistent with that previously reported.
mL), (R,R)-MeBPE-Rh(I) (1 mg), 60 psi H₂ using Method 2 gave 3a, yield 78% (and 6a, yield 17%), HPLC (for 3a): tᵣ = 43 min, 12% e.e. ([R], [α]D = -6.8 (c 2.0, CHCl₃)).

Compound 3a: White solid, mp 94–96°C (lit.¹ᵃ 95–97°C); ¹H NMR (400 MHz, CDCl₃) δ 1.39 (d, 3H, J = 7.1 Hz, 3'-CH₃), 3.24 (m, 1H, 2'-CH), 3.77 (dd, 1H, J = 13.7, 7.0 Hz, NC(H)), 4.01 (dd, 1H, J = 13.7, 8.3 Hz, NC(H)), 7.76 (m, 2H, ArH), 7.88 (m, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃) δ 15.6 (C-3), 25.2 (C-2), 40.1 (C-1'), 120.4 (CN), 123.7 (C-4'/7), 131.6 (C-3a/7a), 134.4 (C-5/6), 167.7 (CO). ¹H NMR spectral data were consistent with that previously reported.¹ᵃ

4.6.2. 2-(2'-Cyanobutyl)phthalimide 3b. (a) (E)-2-(2'-Cyanobut-2'-enyl)phthalimide 1b (32 mg), ethyl acetate (4 mL), Pd/CaCO₃ (10 mg) using Method 1 gave 3b, yield 88% (after recrystallisation from methanol), HPLC: tᵣ = 33 and 39 min (Chiralcel OB, flow rate = 1 mL/min, detection at 254 nm, eluent = 90% hexane:10% 2-propanol). (b) Compound 1b (140 mg), methanol (5 mL), (R,R)-EtDuPHOS-Rh(I) (2 mg), 100 psi H₂, 40°C using Method 2 gave 3b, yield 88%, HPLC: tᵣ = 39 min, 33% e.e., [α]D = +1.0 (c 2.0, CHCl₃).

Compound 3b: White solid, mp 66–70°C (lit.¹ᵃ 65–70°C); ¹H NMR (400 MHz, CDCl₃) δ 1.16 (t, 3H, J = 7.4 Hz, 4'-CH₃), 1.71 (m, 2H, 3'-CH₂), 3.13 (m, 1H, 2'-CH), 3.79 (dd, 1H, J = 13.7, 7.0 Hz, NC(H)), 4.03 (dd, 1H, J = 13.7, 8.4 Hz, NC(H)), 7.76 (m, 2H, ArH), 7.89 (m, 2H, ArH); ¹³C NMR (75 MHz, CDCl₃) δ 11.2 (C-4), 23.2 (C-3'), 32.8 (C-2'), 38.7 (C-1'), 119.5 (CN), 123.7 (C-4'/7), 131.7 (C-3a/7a), 134.4 (C-5/6), 167.7 (CO). ¹H NMR spectral data were consistent with the literature.¹ᵃ

4.6.3. 2-(2'-Cyano-3'-phenylethyl)phthalimide 3c. (a) (E)-2-(2'-Cyano-3'-phenylprop-2'-enyl)phthalimide 1c (84 mg), ethyl acetate (7 mL), Pd/CaCO₃ (31 mg) using Method 1 gave 3c, yield 70% (after chromatography and recrystallisation from ethanol), HPLC: tᵣ = 33 and 49 min (Chiralcel OB, flow rate = 1.5 mL/min, detection at 254 nm, eluent = 80% hexane:20% 2-propanol). (b) Compound 1c (130 mg), methanol (4 mL), (R,R)-EtDuPHOS-Rh(I) (2 mg), 100 psi H₂, 40°C using Method 2 gave 3c, yield 78%, HPLC: tᵣ = 49 min, 3% e.e., [α]D = 0.0 (c 2.0, CHCl₃).

Compound 3c: White solid, mp 114–116°C (lit.¹ᵃ 114–116°C); ¹H NMR (400 MHz, CDCl₃) δ 2.99 (m, 2H, 3'-CH₂), 3.48 (m, 1H, 2'-CH), 3.84 (dd, 1H, J = 13.8, 6.7 Hz, NC(H)), 4.06 (dd, 1H, J = 13.8, 8.6 Hz, NC(H)), 7.29 (m, 5H, ArH), 7.73 (m, 2H, ArH(1)), 7.85 (m, 2H, ArH(2)); ¹³C NMR (100 MHz, CDCl₃) δ 32.9 (C-2'), 36.2 (C-3'), 38.9 (C-1'), 119.2 (CN), 123.7 (C-4'/7), 127.5, 128.86, 128.89 (ArCH), 131.7 (C-3a/7a), 134.4 (C-5/6), 135.7 (ArC), 167.7 (CO). ¹H NMR spectral data were consistent with reported data.¹ᵃ

4.6.4. 2 - [3' - (r - Butyldimethylsilyl) - 2' - cyano-prop-2-enyl]phthalimide 3d. (a) (E)-2-[3' -(r-Butyldimethylsilyl)-2'-cyano-prop-2-enyl]phthalimide 1d (100 mg), ethyl acetate (7 mL), Pd/CaCO₃ (30 mg) using Method 1 gave 3d, yield 93%, HPLC: tᵣ = 10 and 12 min (Chiralcel OD, flow rate = 1 mL/min, detection at 254 nm, eluent = 95% hexane:5% 2-propanol). (b) Compound 1d (110 mg), benzene (5 mL), (R,R)-EtDuPHOS-Rh(I) (1 mg), 100 psi H₂, 40°C using Method 2 gave 3d, yield 84%, HPLC: tᵣ = 10 min, 48% e.e., [α]D = -8.3 (c 2.0, CHCl₃).

Compound 3d: White solid, mp 83.5–86°C; IR: ν = 2926, 2854, 2220, 1768, 1704, 1464, 1398, 1377, 1366, 776, 716 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.10 (s, 3H, SiCH₃), 0.88 (dd, 1H, J = 14.7, 4.9 Hz, SiCH₃(1)), 0.92 (s, 9H, (CH₃)₃C), 1.01 (dd, 1H, J = 14.7, 10.7 Hz, Si(CH₃)H), 3.19 (m, 1H, 2'-CH), 3.71 (dd, 1H, J = 13.6, 6.1 Hz, NC(H)), 4.05 (dd, 1H, J = 13.6, 9.6 Hz, NC(H)), 7.75 (m, 2H, ArH), 7.89 (m, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃) δ 12.9 (CN), 123.7 (C-4'/7), 131.8 (C-3a/7a), 134.4 (C-5/6), 167.8 (CO); MS (EI): m/z = 328 (M⁺, 2%), 327 (5), 281 (20), 272 (21), 29 (29), 160 (10), 130 (10), 73 (16), 44 (10).
1556, 1456, 1440, 1376, 1293, 1144, 1115 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\), \(\delta\) 1.31 (d, 3H, \(J = 7.1\) Hz, 3-\(\text{CH}_3\)), 2.02 (s, 3H, \(\text{OCH}_3\)), 2.98 (m, 1H, \(\text{H}}, \(2921, 2853, 1775, 1731, 1707, 1463, 1398, 1376, 1358, 17a\)
\(13.8, 7.6\) Hz, NCH(H)), 3.97 (dd, 1H, \(J = 13.8, 6.8\) Hz, NCH(H)), 3.78 (dd, 1H, \(J = 13.8, 6.8\) Hz, NCH(H)), 3.97 (dd, 1H, \(J = 13.8, 7.6\) Hz, NCH(H)), 7.72 (m, 2H, ArH), 7.85 (m, 2H, ArH); \(^{13}\)C NMR (75 MHz, CDCl\(_3\), \(\delta\) 14.7 (CH\(_3\)), 38.5 (C-2), 40.6 (C-3), 52.0 (OCH\(_3\)), 123.4 (C-4'/7'), 132.0 (C-3a'/7a'), 134.1 (C-5'/\(6\)), 168.1, 174.3 (CO); MS (EI): \(m/z\) 247 (M\(^+\), 3%), 217 (1), 188 (13), 187 (40), 161 (11), 160 (100); \(C\(_2\)H\(_3\)NO\(_2\))(247.25) calecd: C, 63.15; H, 5.30; N, 5.67; found: C, 63.28; H, 5.44; N, 5.65%.

4.6.9. (E)-Methyl 2-(phthalimidomethyl)butanoate 17b. (a) (E)-Methyl-2-(phthalimidomethyl)but-2-enolate 9b (20 mg), ethyl acetate (3 mL), Pd/CaCO\(_3\) (5 mg) using Method 1 gave 17b, yield 89%, HPLC: \(t_R = 50\) and 59 min (Chiralcel OJ, flow rate = 1.5 mL/min, detection at 254 nm, eluent = 100% hexane). (b) Compound 9b (30 mg), methanol (4 mL), (S)-(BINAP-Ru(II) (1 mg), 90 psi H\(_2\), 100°C, 40 h using Method 2 gave 17b, yield 91%, HPLC: \(t_R = 50\) min, 10% e.e., [\(\alpha\)]\(D\) 0.0 (c 1.0, CHCl\(_3\)).

Compound 17b: White solid, mp 81–83°C, IR: \(\nu = 2926, 2856, 1772, 1724, 1463, 1396, 1377, 1356, 1176, 1045, 722\) cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\), \(\delta\) 0.96 (t, 3H, \(J = 7.4\) Hz, 2-CH\(_3\)), 1.64 (m, 2H, 3-CH\(_2\)), 2.82 (m, 1H, 2-CH), 3.66 (s, 3H, \(\text{OCH}_3\)), 3.81 (dd, 1H, \(J = 13.8, 6.2\) Hz, NCH(H)), 3.95 (dd, 1H, \(J = 13.8, 8.0\) Hz, NCH(H)), 7.71 (m, 2H, ArH), 7.84 (m, 2H, ArH); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), \(\delta\) 11.4 (C-4), 22.9 (C-3), 39.3 (NCH\(_3\)), 46.0 (C-2), 51.9 (OCH\(_3\)), 123.4 (C-4'/7'), 132.0 (C-3a'/7a'), 134.0 (C-5'/\(6\)), 168.1, 173.9 (CO); MS (EI): \(m/z\) 261 (M\(^+\), <1%), 230 (4), 201 (50), 186 (11), 160 (100), 133 (10), HRMS (EI): \(m/z\) calecd for \(C\(_{14}\)H\(_{15}\)NO\(_4\)): 261.1001; found: 261.1002.

4.7. Hydrolysis to \(\alpha\)-methyl-\(\beta\)-alanine 12 (3-amino-2-methylpropanoic acid)

Using a similar procedure to that described by Galat,\(^{20}\) 3a, 18 or 17a (ca. 60 mg) and 6 M HCl (3 mL) were stirred under reflux for 15–24 h. The solution was cooled and the precipitated phthalic acid was filtered off. The filtrate was evaporated to dryness and the resultant solid was dissolved in hot 2-propanol and the NH\(_4\)Cl removed by filtration. Removal of the 2-propanol gave the amino acid hydrochloride 11 which was dissolved in water and passed through an ion exchange column (IR-4B Amberlite resin). Removal of the water gave the free amino acid 12 together with some phthalic acid as a pale yellow hygroscopic solid.

4.7.1. (S)-\(\alpha\)-Methyl-\(\beta\)-alanine 12. (a) 2-(2'-Cyano-2-propenylphthalimide 3a (sample having [\(\alpha\)]\(D\) +8.3, 14% e.e, see Section 4.6.1.b) (60 mg) gave 12, yield 58%; [\(\alpha\)]\(D\) (corrected for chemical conversion) +19.0 (c 0.42, D\(_2\)O), (S)-enantiomer. (b) N-(2'-Cyano-2-propenyl)acetamide 18 (sample having [\(\alpha\)]\(D\) +77.8, 64% e.e., see Section 4.6.6) (63 mg) gave 12, yield 88%, [\(\alpha\)]\(D\) +7.6 (c 0.42, H\(_2\)O), (S)-enantiomer.

4.7.2. (R)-\(\alpha\)-Methyl-\(\beta\)-alanine 12. Methyl 2-methyl-3-phthalimidopropanoate 17a (sample having [\(\alpha\)]\(D\) -16.9, 80% e.e, see Section 4.6.8) (49 mg) gave 12, yield 90%, [\(\alpha\)]\(D\) (corrected for chemical conversion) -8.2 (c 0.42, D\(_2\)O), (R)-enantiomer.
Compound 12: 1H NMR (400 MHz, D2O) δ 1.18 (d, 3H, J = 7.3 Hz, CH3), 2.64 (m, 1H, 2-CH), 3.03 (dd, 1H, J = 12.9, 5.3 Hz, NCH(CH3)), 3.11 (dd, 1H, J = 12.9, 8.4 Hz, NC(H(H))); 13C NMR (100 MHz, D2O) δ 15.0 (CH3), 38.8 (C-2), 42.3 (C-3), 180.8 (CO); MS (EI): m/z 103 (M+ 8%), 89 (86), 87 (100), 85 (11), 83 (17), 78 (11), 55 (30), 44 (12), 43 (40) (lit.9 [x]D − 14.0 (c 0.42, D2O) for the (R)-enantiomer).

4.8. Preparation of N-benzoyl derivatives of 12

4.8.1. 3-(Benzoylamino)-2-methylpropanoic acid. A solution of α-methyl-β-alanine hydrochloride (11) (240 mg, 2.35 mmol) in aqueous NaOH (2 M, 4 mL) was treated with benzoyl chloride (0.38 mL, 3.29 mmol) and allowed to stir at ambient temperature overnight. The solution was extracted with dichloromethane (10 mL) and the solution cooled at 0°C before the slow addition of chlorotriethylsilane (61 mL). The organic extracts were washed with brine (15 mL), dried (MgSO4), filtered and evaporated to dryness. The crude was purified by flash chromatography (ethyl acetate:light petroleum:acetic acid, 4:6:1) to give the benzoyl derivative as a clear, colourless oil which solidified on standing, yield 27%; IR: v = 3448, 3054, 2986, 1708, 1604, 1579, 1522, 1486, 1465, 1422, 1154 cm−1; 1H NMR (200 MHz, CDCl3) δ 1.27 (d, 3H, J = 7.2 Hz, CH3), 2.85 (m, 1H, 2-CH), 3.51 (m, 1H, NCH(CH3)), 3.74 (m, 1H, NCH(NH)), 6.95 (bs, 1H, NH), 7.45 (m, 3H, ArH), 7.75 (m, 2H, ArH); 13C NMR (50 MHz, CDCl3) δ 14.9 (CH3), 39.6 (C-2), 42.1 (C-3), 127.1, 128.7, 131.8 (ArCH), 134.2 (ArC), 168.2 (CO); MS (EI): m/z 207 (M+ 3%), 189 (2), 161 (15), 122 (30), 105 (62). HRMS (EI): m/z calcd for C11H15NO4: 207.0895; found: 207.0901.

4.8.2. Ethyl 3-(Benzoylamino)-2-methylpropanoate 14. Method A: Ethyl iodide (28 µL, 0.35 mmol) was added to a solution of racem 3-(Benzoylamino)-2-methylpropanoic acid (prepared from racemic α-methyl-β-alanine) (50 mg, 0.29 mmol) and freshly distilled 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (52 µL, 0.35 mmol) in benzene (5 mL) and the solution was heated at reflux for 15 h. Water (10 mL) was added and the mixture extracted with diethyl ether (3×10 mL), dried over MgSO4, filtered and the solvent removed in vacuo over MgSO4, filtered and the solvent removed in vacuo to give a yellow oil. Flash chromatography (ethyl acetate:light petroleum:acetic acid, 2:8:1) gave the ester 14, yield 72%; HPLC: tr = 59 min, 11% e.e., (S)-enantiomer, [x]D +3.1 (c 1.0, CHCl3). (b) (S)-α-Methyl-β-alanine 12 (prepared as described in Section 4.7.1 from a sample of nitrile 3a having an [x]D +8.3 (120 mg) using Method B gave 14, yield 78%, [x]D +3.4 (c 1.0, CHCl3).

Compound 14: Yellow viscous oil; IR: v = 3331, 2981, 2938, 1732, 1644, 1603, 1580, 1538, 1490, 1463, 1380, 1310, 1258, 1190, 1135, 1096, 1076, 1024, 713, 695 cm−1; 1H NMR (200 MHz, CDCl3) δ 1.24 (d, 3H, J = 7.3 Hz, CH3), 1.27 (t, 3H, J = 7.2 Hz, CH3CH2); 2.81 (m, 1H, 2-CH), 3.51 (m, 1H, NCH(NH)), 3.71 (m, 1H, NCH(NH)), 4.17 (q, 2H, J = 7.1 Hz, 2H, CH2CH2), 6.91 (bs, 1H, NH), 7.46 (m, 3H, ArH), 7.77 (m, 2H, ArH); 13C NMR (50 MHz, CDCl3) δ 14.3, 15.0 (CH3, CH2CH3), 39.6 (C-2), 42.1 (C-3), 60.9 (CH2CH3), 127.0, 128.6, 131.5 (ArCH), 134.5 (ArC), 167.5 (COPh), 175.9 (CO2); MS (EI): m/z 235 (M+ 10%), 190 (17), 134 (10), 105 (100), 75 (10), 76 (13); HRMS (EI): m/z calcd for C13H16NO3: 235.1208; found: 235.1205.

4.9. 3-[(9H-Fluoren-9-ylmethoxy)carbonyl]amino)-2-methylpropanoic acid 13

α-Methyl-β-alanine hydrochloride (11) (0.92 g, 8.96 mmol) and sodium iodide (1.66 g, 15.68 mmol) were suspended in water (25 mL) and acetone (20 mL) and the mixture cooled in ice with stirring. A solution of N-(9-fluorenylmethoxy)carbonyl)succinimide (Fmoc-Osu) (3.02 g, 8.96 mmol) in acetone (15 mL) was added dropwise. The mixture was stirred at 4°C for 20 min and at ambient temperature for 4 h. The solution was acidified to pH 3–4 with concentrated HCl and extracted with ethyl acetate (3×30 mL). The organic extracts were combined, washed with water (2×30 mL), brine (20 mL), dried over MgSO4, filtered and evaporated to dryness to give a white solid (1.80 g). Purification by flash chromatography (ethyl acetate:light petroleum:acetic acid, 2:8:1) gave 13, yield 35%.

(a) Reaction of α-methyl-β-alanine 12 (sample having an [x]D +19.0, see Section 4.7.1.a) (100 mg) with Fmoc-Osu (330 mg) as described above gave 13, yield 35%; [x]D +25.5 (c 1.0, CH2Cl2) (S)-enantiomer (lit.12 [x]D +9 (c 1.0, CH2Cl2) (S)-enantiomer. (b) An identical reaction of a freshly prepared sample of 12 gave 13, yield 33%; [x]D +2.5 (c 1.0, CH2Cl2).

Compound 13: White solid; mp 165.5–168°C (lit.12 165.5–168°C); IR: ν = 3337, 2924, 2854, 1692, 1544, 1460, 1377, 1273, 1221, 1159, 1006, 758, 742, 734 cm−1; 1H NMR (300 MHz, CD3OD) δ 0.99 (m, 3H, CH3), 2.60 (sept, 1H, J = 7.0 Hz, 2-CH2), 3.16 (dd, 1H, J = 13.5, 6.4 Hz, NCH(NH3)), 3.33 (dd, 1H, J = 13.6, 6.5 Hz, NCH(NH4), 4.16 (m, 1H, 9'-CH), 4.30 (m, 2H, OCH2), 4.47 (bs, 1H, NH); 13C NMR (75 MHz, CD3OD) δ 12.7 (CH3), 38.6 (C-9'), 42.2 (C-3), 46.1 (C-2), 65.3 (OCH3), 118.5, 123.7, 125.7, 126.3 (C-1'-'8'), 140.2 (C-4a/-4b), 142.9 (C-8a/-9a), 156.5 (CO-Fmoc), 176.2 (CO2H); MS (EI): m/z 325 (M+ 1%), 237 (1), 178 (100), 166 (61), 163 (31), 70 (25).
4.10. Reactions with deuterium

Reactions of the nitriles 1a and 1b with deuterium were carried out as described for hydrogenation reactions in Section 4.6, Method 2.

4.10.1. (2′-H1,3′-H2)–2-(2′-Cyanopropyl)phthalimide 16a. Reaction of 2-(2′-cyano-2-propenyl)phthalimide 1a (260 mg, 1.24 mmol), methanol (10 mL) and (R,R)-EtDuPHOS-Rh(I) (5 mg) with deuterium (70 psi) at 40°C gave 16a as a white solid after chromatography, yield 81%; IR: v = 2923, 2854, 2243, 1777, 1715, 1464, 1435, 1394, 1378, 1354, 973, 720 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 1.37 (bs, 2H, CH₂D), 3.75 (d, 1H, J = 13.7 Hz, NCH(H)), 7.76 (m, 2H, ArH), 7.88 (m, 2H, ArH); 2H NMR (61.4 MHz, CDCl₃) found: 230.1026; [z]D +1.2 (c 2.0, CHCl₃).

Acknowledgements

The authors would like to thank the Australian Research Council for support and provision of an Australian Postgraduate Research Award (to D.S.), Johnson Matthey Pty Ltd for a loan of precious metals and Professor Dieter Seebach, ETH, for his helpful comments and Dr. Stefan Abele, ETH, for comparison of the properties of the Fmoc derivative 13 with an authentic sample.

References