



## A new enantioselective synthesis of $\beta$ -amino acids

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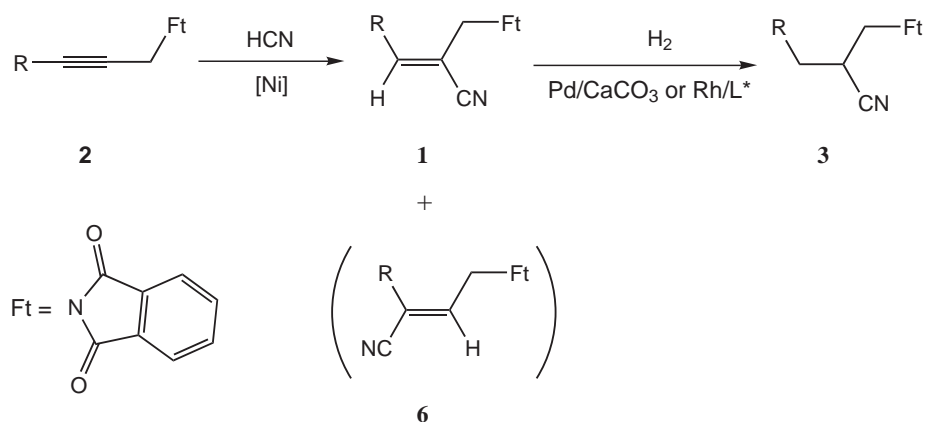
**Abstract**—Enantioselective hydrogenation of some  $\alpha,\beta$ -unsaturated nitriles and their corresponding methyl esters bearing a phthalimidomethyl substituent at the  $\alpha$ -carbon using Rh-DuPHOS catalysts afforded  $\beta$ -amino acid precursors with modest e.e.s of up to 48%. Hydrogenation of the  $\alpha,\beta$ -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  $\alpha$ -phthalimidomethyl substituent **1** can be prepared by the nickel-catalysed addition of hydrogen cyanide (**CAUTION**)<sup>†</sup> to appropriate alkynes **2** and hydrogenated over Pd/CaCO<sub>3</sub> to give  $\beta$ -amino acid precursors **3**<sup>1</sup> (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.<sup>2–4</sup> It has been established that enantioselective Rh-catalysed reactions of  $\alpha$ -*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).<sup>5</sup> 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.

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<sup>†</sup> Use of HCN is hazardous and suitable precautions for use and disposal must be taken.

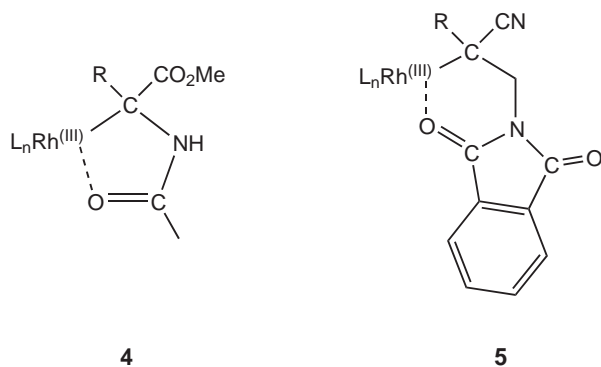


Figure 1.



Figure 2.

propargylamino derivatives but none of these systems appear to have been evaluated in enantioselective routes to  $\beta$ -amino acid precursors.

Three catalysts were chosen for evaluation in this study, the Ru-BINAP<sup>6</sup> and the Rh-DuPHOS<sup>7</sup> and the closely related Rh-BPE system.<sup>7</sup> The Rh-DuPHOS and Rh-BPE catalysts are known to produce excellent enantioselectivities for the hydrogenation of  $\alpha$ -amino acid precursors and the Ru-BINAP system has previously been used to give  $\beta$ -amino acids with high enantioselectivity in the hydrogenation of (*E*)- $\beta$ -(acylamino)acrylic acids, these methodologies are different from the study reported herein.<sup>8</sup>

## 2. Results and discussion

### 2.1. Preparation of substrates

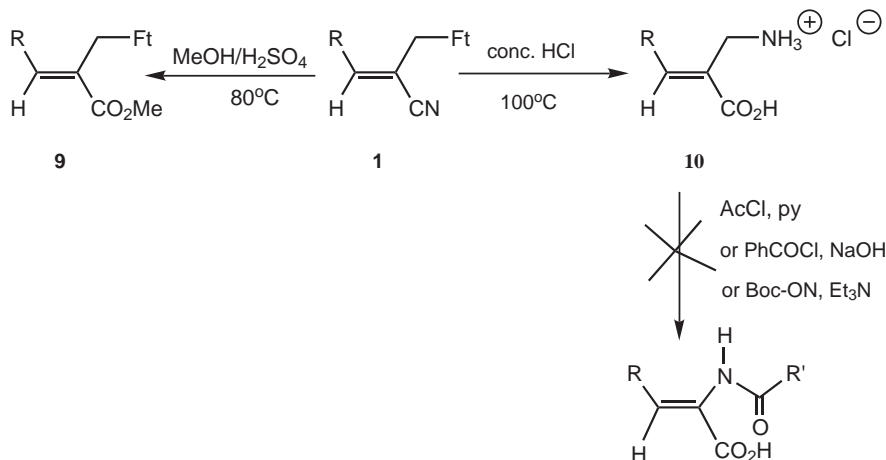
Substrates **1** were prepared by Ni[P(OPh)<sub>3</sub>]<sub>4</sub>-catalysed addition of hydrogen cyanide to the alkynes **2**. Compounds **1a–1c** have been prepared previously and similar yields of **1** together with similar percentages of the undesired isomers **6** were obtained.<sup>1</sup> Hydrocyanation 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 H<sub>2</sub> (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 MeOH 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.

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

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

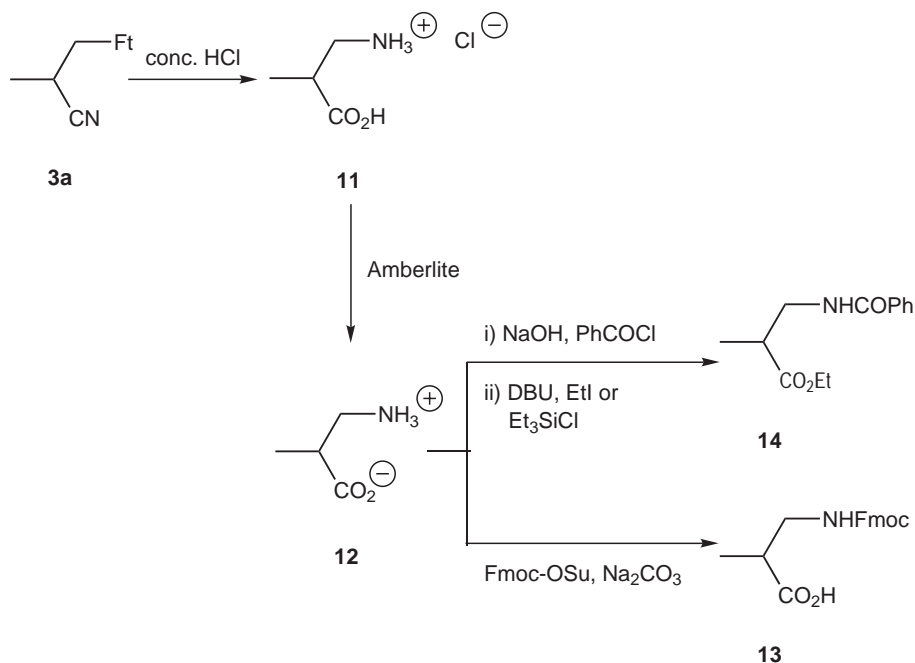
<sup>a</sup> Reductions for 24 h.<sup>b</sup> Enantiomeric excess determined by HPLC (see below).<sup>c</sup> Isolated yield after chromatography.<sup>d</sup> (*R,R*)-Et-DuPHOS-Rh(I).<sup>e</sup> (*R,R*)-Me-BPE-Rh(I).

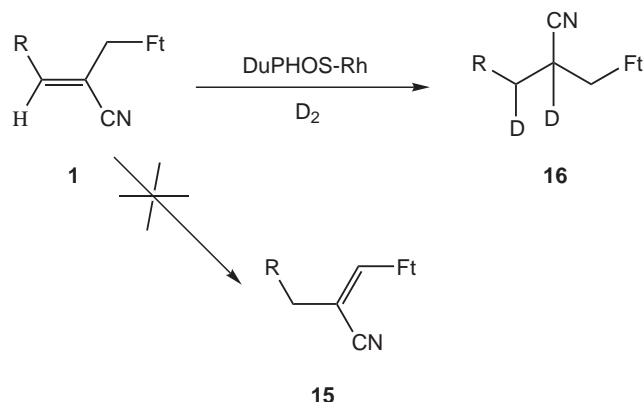
A sample of the product **3a** with  $[\alpha]_D$  +8.3 was hydrolysed using conc. HCl to give a sample of the hydrochloride salt of  $\alpha$ -methyl- $\beta$ -alanine **11** which was converted to the free amino acid **12** by passing through an Amberlite column (Scheme 3).

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<sup>9,10</sup> have been recorded under identical conditions, i.e.  $c$ =0.42 in H<sub>2</sub>O, 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.<sup>7c</sup> 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

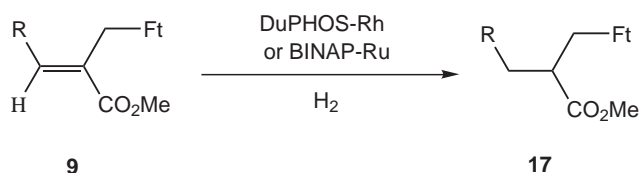
phosphine ligand, for example from Me, Et and *n*-Pr to *i*-Pr in the case of DuPHOS, can lead to a change in the absolute configuration of the product.<sup>7c</sup>

The inconsistencies in using the specific rotation values of free amino acids as measures of enantioselectivity are well known<sup>11</sup> 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.<sup>12</sup> 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-

**Scheme 3.**



Scheme 4. R = a, H; b, Me.



Scheme 5. R = a, H; b, Me

appointing 11% and the possibility of racemisation during the hydrolysis of the phthalimido nitrile **3a** or the formation of the *N*-benzoyl ethyl ester **14** was considered. Extensive experimentation finally led to conditions which allowed HPLC resolution of the phthalimido nitrile **3a** using a Chiralcel OB column. An e.e. value of 14% was obtained showing that no significant racemisation had occurred and that only low enantioselectivity had been obtained in the hydrogenation reaction.

Attempted hydrogenation of **1a** using (*S*)-BINAP-Ru(II) in MeOH under similar conditions (20°C, 50 psi) failed to give any saturated product.

Similar hydrogenations of the substituted phthalimido nitriles **1b–1e** (Scheme 1) were carried out and the enantioselectivities measured by HPLC using Chiralcel OB or OD columns (Table 1, entries 5–8). Modest e.e.s of 33% for the methyl (entry 5) and 48% for the TBDMS (entry 7) derivatives **3b** and **3d** were obtained. The phenyl derivative **3c** was obtained in only 3% e.e., a surprising result in view of the successful hydrogenation of cinnamate derivatives.<sup>2</sup>

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.<sup>2</sup> 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<sub>2</sub> adjacent to the phthalimido group (Scheme 4). The <sup>1</sup>H, <sup>2</sup>H and <sup>13</sup>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  $\alpha$ -<sup>7,13</sup> and  $\beta$ -amido<sup>8,14</sup> substituents or an  $\alpha$ -CH<sub>2</sub>CO<sub>2</sub>Me substituent.<sup>15</sup>

Hydrogenation of **9a** using BINAP-Ru at ambient temperature with a H<sub>2</sub> 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<sub>2</sub>O), again within the range of values previously reported.<sup>9–11</sup> 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.<sup>16</sup> 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%

Table 2. Enantioselective hydrogenation of  $\alpha,\beta$ -unsaturated phthalimido esters **9**<sup>a</sup>

Entry	Substrate <b>9</b> , R =	Catalyst <sup>b</sup>	Temp. (°C)	Pressure (psi)	$[\alpha]_D$	e.e. <sup>c</sup> (%)	Yield <sup>d</sup> (%)
9	<b>9a</b> , H	BINAP-Ru	20	100	−16.9	80	92
10	<b>9a</b> , H	BINAP-Ru	20	50	−17.2	84	91
11	<b>9a</b> , H	DuPHOS-Rh	20	50	+6.3	12	93
12	<b>9b</b> , Me	BINAP-Ru	100	90	0.0	10	91

<sup>a</sup> Reactions in MeOH for 40 h.

<sup>b</sup> (*S*)-BINAP-Ru(II); (*R,R*)-Et-DuPHOS-Rh(I).

<sup>c</sup> Enantiomeric excess determined by HPLC (see below).

<sup>d</sup> Isolated yield after chromatography.



Figure 3.

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  $[\alpha]_D +7.6$ . 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 ( $^1\text{H}$ ) and 50 ( $^{13}\text{C}$ ) MHz, on a Bruker DPX-300 spectrometer operating at 300 ( $^1\text{H}$ ) and 75 ( $^{13}\text{C}$ ) MHz, or on a Bruker DRX-400 spectrometer operating at 400 ( $^1\text{H}$ ), 100 ( $^{13}\text{C}$ ) and 61.4 ( $^2\text{H}$ ) MHz using either  $\text{Me}_4\text{Si}$  ( $^1\text{H}$ ) or the solvent peak ( $^{13}\text{C}$ ,  $^2\text{H}$ ) 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  $\mu\text{m}$  (230–400 mesh) silica gel 60 (Merck

no. 9385). Analytical thin-layer chromatography (TLC) was performed on Polygram Sil G/UV<sub>254</sub> 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 Å, 3.9 mm×30 cm, 10  $\mu\text{L}$ ), 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×25 cm with a particle size of 10  $\mu\text{m}$ . 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. (–)-1,2-Bis[(2*R*,5*R*)-2,5-diethylphospholano]benzene(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate [(*R,R*)-EtDuPHOS-Rh(I)] and (*R,R*)-(–)-1,2-bis[*o*-methoxyphenyl](phenyl)phosphino]ethane(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate [(*R,R*)-MeBPE-Rh(I)] were used as supplied from Strem Chemicals. [(*S*)-(–)-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<sub>3</sub>) 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**, *N*-(prop-2-ynyl)-acetamide and *tert*-butyl *N*-(prop-2-ynyl)carbamate were prepared as described in the literature.<sup>1a</sup>

**4.2.1. *N* - [3' - (*t* - Butyldimethylsilyl)prop - 2' - ynyl]phthalimide **2d**.** Compound **2d** was prepared from the corresponding alcohol as described by Landini<sup>17</sup> and recrystallised from ethanol as colourless crystals (yield:

89%); mp 136.5–137.5°C; IR:  $\nu$  = 2926, 2855, 2181, 1774, 1714, 1612, 1464, 1419, 1393, 1319, 1252, 1117, 1037, 939, 835, 775, 724, 713, 680  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  0.06 (s, 6H,  $\text{Si}(\text{CH}_3)_2$ ), 0.89 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ), 4.46 (s, 2H,  $1'\text{-CH}_2$ ), 7.71–7.77 (m, 2H, ArH), 7.85–7.90 (m, 2H, ArH);  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  -4.7 ( $\text{Si}(\text{CH}_3)_2$ ), 16.6 ( $\text{C}(\text{CH}_3)_3$ ), 26.1 ( $\text{C}(\text{CH}_3)_3$ ), 28.1 (C-1'), 85.5 (C-3'), 99.3 (C-2'), 123.6 (C-4/7), 132.1 (C-3a/7a), 134.2 (C-5/6), 167.0 (CO); MS (EI):  $m/z$  (no  $\text{M}^+$ ), 284 ( $\text{M}-15$ , 1%), 242 (100), 130 (50), 102 (22);  $\text{C}_{17}\text{H}_{21}\text{NO}_2\text{Si}$  (299.45) calcd: C, 68.2; H, 7.1; N, 4.7; found: C, 68.4; H, 7.2; N, 4.4%.

**4.2.2. *N*-[3'-(Trimethylsilyl)prop-2'-ynyl]phthalimide 2e.** Compound **2e** was prepared as above and recrystallised from ethanol as colourless crystals (yield: 74%); mp 125–126.2°C; IR:  $\nu$  = 2924, 2854, 2181, 1770, 1465, 1429, 1393, 1379, 1353, 1328, 1252, 1122, 1028, 950, 848, 732, 652  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  0.12 (s, 9H,  $\text{Si}(\text{CH}_3)_3$ ), 4.45 (s, 2H,  $1'\text{-CH}_2$ ), 7.71 (m, 2H, ArH), 7.87 (m, 2H, ArH);  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  -0.1 ( $\text{Si}(\text{CH}_3)_3$ ), 28.1 (C-1'), 88.3 (C-3'), 98.6 (C-2'), 123.3 (C-4/7), 132.2 (C-3a/7a), 134.3 (C-5/6), 167.1 (CO); MS (EI):  $m/z$  257 ( $\text{M}^+$ , 5%), 243 (20), 242 (100), 163 (11), 130 (74), 104 (14), 102 (50), 77 (17), 76 (36), 73 (23), 50 (11);  $\text{C}_{14}\text{H}_{15}\text{NO}_2\text{Si}$  (257.37) calcd: C, 65.4; H, 5.9; N, 5.4; found: C, 65.4; H, 6.1; N, 5.5%.

### 4.3. General procedure for hydrocyanation reactions

All hydrocyanation reactions were carried out in a 75 mL stainless steel autoclave as described previously.<sup>1,18</sup> The substrate (5 mmol), catalyst ( $\text{Ni}[\text{P}(\text{O}Ph)_3]_4$  (100  $\mu\text{mol}$ ), ligand ( $\text{P}(\text{O}Ph)_3$  (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 in vacuo to give the crude product. Flash chromatography (silica, ethyl acetate/light petroleum) gave the product nitriles.

**4.3.1. 2-(2'-Cyanoprop-2'-enyl)phthalimide 1a<sup>1a</sup>.** 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;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  39.6 (C-1'), 116.6 (C-2'), 118.0 (CN), 123.8 (C-4/7), 131.7 (C-3'), 132.9 (C-3a/7a), 134.5 (C-5/6), 167.1 (CO).  $^1\text{H}$  NMR spectral data were consistent with the literature.<sup>1a</sup>

**4.3.2. (*E*)-2-(2'-Cyanobut-2'-enyl)phthalimide 1b<sup>1a</sup>.** Yield: 44%;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  14.8 (C-4'), 34.6 (C-1'), 111.2 (C-2'), 118.0 (CN), 123.6 (C-4/7), 131.8 (C-3a/7a), 134.3 (C-5/6), 147.0 (C-3'), 167.3 (CO).

**4.3.3. (*E*)-2-(2'-Cyano-3'-phenylprop-2'-enyl)phthalimide 1c<sup>1a</sup>.** Yield: 58%;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  36.1 (C-1'), 111.1 (C-2'), 117.9 (CN), 123.7 (C-4/7), 128.9, 129.4, 130.0 (ArCH), 131.8 (C-3a/7a), 133.1 (ArC), 134.3 (C-5/6), 146.5 (C-3'), 167.3 (CO).

**4.3.4. (*E*)-2-[3'-(*t*-Butyldimethylsilyl)-2'-cyanoprop-2'-enyl]phthalimide 1d.** Yield: 75%; mp 125–128°C; IR:  $\nu$  = 2923, 2854, 2206, 1771, 1722, 1463, 1378, 1341, 1309, 1252, 950, 852, 826, 711  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.32 (s, 6H,  $\text{Si}(\text{CH}_3)_2$ ), 0.98 (s, 9H,  $(\text{CH}_3)_3\text{C}$ ), 4.52 (d, 2H,  $J$  = 1.6 Hz,  $1'\text{-CH}_2$ ), 6.81 (t, 1H,  $J$  = 1.5 Hz,  $3'\text{-CH}$ ), 7.75 (m, 2H, ArH), 7.88 (m, 2H, ArH);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  -4.9 ( $\text{Si}(\text{CH}_3)_2$ ), 17.1 ( $(\text{CH}_3)_3\text{C}$ ), 26.2 ( $(\text{CH}_3)_3\text{C}$ ), 39.2 (C-1'), 117.5 (CN), 123.7 (C-4/7), 125.2 (C-2'), 131.8 (C-3a/7a), 134.3 (C-5/6), 150.8 (C-3'), 167.3 (CO); MS (EI):  $m/z$  326 ( $\text{M}^+$ , 1%), 311 (3), 270 (19), 269 (100), 242 (4), 130 (70), 102 (27), 75 (27), 57 (23);  $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_2\text{Si}$  (323.45) calcd: 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'-Cyano-3'-(trimethylsilyl)prop-2'-enyl]phthalimide 1e.** Yield: 70%; mp 82–84.5°C; IR:  $\nu$  = 2925, 2854, 2211, 1771, 1719, 1465, 1430, 1390, 1343, 1311, 1253, 1190, 1122, 948, 865, 848, 737, 711  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.32 (s, 9H,  $\text{Si}(\text{CH}_3)_3$ ), 4.50 (d, 2H,  $J$  = 1.4 Hz, 1H,  $1'\text{-CH}_2$ ), 6.77 (t,  $J$  = 1.3 Hz, 1H,  $3'\text{-CH}$ ), 7.74 (m, 2H, ArH), 7.86 (m, 2H, ArH);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  -0.7 ( $\text{Si}(\text{CH}_3)_3$ ), 39.1 (C-1'), 117.5 (CN), 123.7 (C-4/7), 123.8 (C-2'), 131.8 (C-3a/7a), 134.3 (C-5/6), 153.1 (C-3'), 167.3 (CO); MS (EI):  $m/z$  284 ( $\text{M}^+$ , 3%), 283 (4), 270 (18), 269 (76), 205 (18), 204 (82), 160 (35), 130 (100), 105 (10), 104 (16), 102 (42), 77 (30), 73 (40), 58 (14);  $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_2\text{Si}$  (284.39) calcd: 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/0.20 mm; IR:  $\nu$  = 3295, 3076, 2936, 2227, 1662, 1548, 1428, 1374, 1289, 1033, 953  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.04 (s, 3H,  $\text{CH}_3$ ), 4.01 (dt, 2H,  $J$  = 6.2, 1.3 Hz,  $1'\text{-CH}_2$ ), 5.95 (t, 1H,  $J$  = 1.5 Hz,  $3'\text{-CH}(E)$ ), 5.99 (t, 1H,  $J$  = 1.2 Hz,  $3'\text{-CH}(Z)$ ), 6.46 (bs, 1H, NH);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  22.9 ( $\text{CH}_3$ ), 41.8 (C-1'), 117.3 (CN), 120.2 (C-2'), 131.6 (C-3'), 170.5 (CO); MS (EI):  $m/z$  124 ( $\text{M}^+$ , 12%), 109 (8), 82 (100), 81 (57), 66 (42), 55 (30), 54 (40), 52 (43), 51 (36); HRMS (EI):  $m/z$  calcd for  $\text{C}_6\text{H}_8\text{N}_2\text{O}$ : 124.0637; found: 124.0636.

**4.3.7. *t*-Butyl *N*-(2'-cyanoprop-2'-enyl)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:  $\nu$  = 3350, 2979, 2930, 2227, 1699, 1516, 1368, 1252, 1170, 1053, 949, 862  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.46 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ), 3.89 (bd, 2H,  $J$  = 6.3 Hz,  $1'\text{-CH}_2$ ), 4.90 (bs, 1H, NH), 5.92 (bt, 1H,  $J$  = 1.5 Hz,  $3'\text{-CH}(E)$ ), 5.98 (t, 1H,  $J$  = 1.3 Hz,  $3'\text{-CH}(Z)$ );  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  28.3 ( $\text{C}(\text{CH}_3)_3$ ), 43.1 (C-1'), 80.4 ( $\text{C}(\text{CH}_3)_3$ ), 117.3 (CN), 121.0 (C-2'), 130.7 (C-3'), 155.3 (CO); MS (EI):  $m/z$  167 ( $\text{M}^+ - \text{CH}_3$ , 9%), 149 (12),



127 (80), 126 (100), 123 (20), 109 (26); C<sub>9</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub> (182.22) calcd: 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).<sup>19</sup> The mixture was stirred under reflux for 6.3 h (for **1a**) or heated at 80°C for 24 h (for **1b**). The solution was cooled and added to an ice-water slurry. Extraction with dichloromethane (3×20 mL) followed by drying (MgSO<sub>4</sub>), filtration and evaporation of the solvent in vacuo gave the alkenoates **9a** and **9b** which were purified by flash chromatography (ethyl acetate:light petroleum, 20:80).

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

White solid, mp 93–96°C; yield: 54%; IR:  $\nu$ =2923, 2854, 1774, 1730, 1709, 1463, 1426, 1394, 1376, 1265, 1196, 1157, 1114, 961, 733, 714 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  3.80 (s, 3H, OCH<sub>3</sub>), 4.56 (t, 2H, *J*=1.5 Hz, NCH<sub>2</sub>), 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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  38.3 (NCH<sub>2</sub>), 52.1 (OCH<sub>3</sub>), 123.5 (C-4'/7'), 126.1 (C-3), 132.0 (C-3a'/7a'), 134.1 (C-5'/6'), 134.5 (C-2), 165.7, 167.7 (CO); MS (EI): *m/z* 214 (M<sup>+</sup>-OCH<sub>3</sub>, 37%), 213 (100), 186 (22), 185 (64), 160 (28), 157 (19), 130 (17), 104 (25), 77 (13), 76 (23), 44 (16); C<sub>13</sub>H<sub>11</sub>NO<sub>4</sub> (245.24) calcd: C, 63.67; H, 4.52; N, 5.71; found: C, 63.40; H, 4.39; N, 5.66%.

##### 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:  $\nu$ =3056, 2988, 2954, 1774, 1720, 1469, 1438, 1397, 1363, 1332, 1202, 1145, 1058 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  2.05 (d, 3H, *J*=7.3 Hz, 4-CH<sub>3</sub>), 3.71 (s, 3H, OCH<sub>3</sub>), 4.58 (s, 2H, NCH<sub>2</sub>), 7.13 (q, 1H, *J*=7.3 Hz, 3-CH), 7.69 (m, 2H, ArH), 7.82 (m, 2H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  14.6 (C-4), 33.9 (NCH<sub>2</sub>), 51.8 (OCH<sub>3</sub>), 123.2 (C-4'/7'), 127.1 (C-2), 132.1 (C-3a'/7a'), 133.8 (C-5'/6'), 143.3 (C-3), 166.8, 167.8 (CO); C<sub>14</sub>H<sub>13</sub>NO<sub>4</sub> (259.26) calcd: C, 64.86; H, 5.05; N, 5.40; found: C, 64.84; H, 5.25; N, 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.<sup>1a</sup> The <sup>1</sup>H NMR spectral data were consistent with that previously reported.<sup>1a</sup>

#### 4.6. Hydrogenation reactions

**Method 1:** Reactions employing Pd/CaCO<sub>3</sub> 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 controlled 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 pressure. The autoclave was tested for leaks, the hydrogen gas was then vented until the desired reaction pressure of 145 psi was achieved and the vessel was heated at 70°C for 16 h. The autoclave was cooled to ambient temperature, the gas was slowly vented, the mixture filtered through a Celite pad and the solvent removed in vacuo. The crude product was purified by flash chromatography (silica, ethyl acetate:light petroleum, 20:80 unless otherwise noted).

**Method 2:** Reactions involving the asymmetric homogeneous 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) 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 chromatography as described above.

Hydrogenation experiments are described in the following format: substrate, solvent, catalyst, hydrogen pressure, 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  $\alpha$ -methyl- $\beta$ -alanine is based on the configuration of the hydrolysed amino acid compared with the absolute configuration of  $\alpha$ -methyl- $\beta$ -alanine **12**. Retention time (*t<sub>R</sub>*) is quoted for the major enantiomer.

**4.6.1. 2-(2'-Cyanopropyl)phthalimide **3a**.** (a) 2-(2'-Cyano-2'-prop-2'-enyl)phthalimide **1a** (30.5 mg), ethyl acetate (4 mL), Pd/CaCO<sub>3</sub> (10.0 mg) using Method 1 gave **3a**, yield 95%, HPLC: *t<sub>R</sub>*=36 and 43 min (Chiralcel OB, flow rate=1 mL/min, detection at 254 nm, eluent=90% hexane:10% 2-propanol. (b) A mixture of 2-(2'-cyanoprop-2'-enyl)phthalimide **1a** and (*E*)-2-(3'-cyanoprop-2'-enyl)phthalimide **6a** (isomer ratio 85:15) (930 mg), methanol (15 mL), (*R,R*)-EtDuPHOS-Rh(I) (10 mg), 70 psi H<sub>2</sub> using Method 2 gave **3a**, yield 86% (and **6a**, yield 13%), HPLC (for **3a**): *t<sub>R</sub>*=36 min, 14% e.e. (*S*), [ $\alpha$ ]<sub>D</sub>+8.3 (c 2.0, CHCl<sub>3</sub>). (c) Nitriles **1a** and **6a** (ratio 85:15) (101 mg), acetonitrile (5 mL), (*R,R*)-EtDuPHOS-Rh(I) (1 mg), 70 psi H<sub>2</sub> using Method 2, gave **3a**, yield 81% (and **6a**, yield 12%), HPLC (for **3a**): *t<sub>R</sub>*=36 min, 4% e.e. (*S*), [ $\alpha$ ]<sub>D</sub>+1.0 (c 2.0, CHCl<sub>3</sub>). (d) Nitriles **1a** and **6a** (ratio 85:15) (114 mg) methanol (5

mL), (*R,R*)-MeBPE-Rh(I) (1 mg), 60 psi H<sub>2</sub> using Method 2 gave **3a**, yield 78% (and **6a**, yield 17%), HPLC (for **3a**): *t*<sub>R</sub> = 43 min, 12% e.e. (*R*), [ $\alpha$ ]<sub>D</sub> –6.8 (*c* 2.0, CHCl<sub>3</sub>).

Compound **3a**: White solid, mp 94–96°C (lit.<sup>1a</sup> 95–97°C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.39 (d, 3H, *J* = 7.1 Hz, 3'-CH<sub>3</sub>), 3.24 (m, 1H, 2'-CH), 3.77 (dd, 1H, *J* = 13.7, 7.0 Hz, NCH(H)), 4.01 (dd, 1H, *J* = 13.7, 8.3 Hz, NCH(H)), 7.76 (m, 2H, ArH), 7.88 (m, 2H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  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). <sup>1</sup>H NMR spectral data were consistent with that previously reported.<sup>1a</sup>

**4.6.2. 2-(2'-Cyanobutyl)phthalimide 3b.** (a) (*E*)-2-(2'-Cyanobut-2'-enyl)phthalimide **1b** (32 mg), ethyl acetate (4 mL), Pd/CaCO<sub>3</sub> (10 mg) using Method 1 gave **3b**, yield 88% (after recrystallisation from methanol), HPLC: *t*<sub>R</sub> = 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 H<sub>2</sub>, 40°C using Method 2 gave **3b**, yield 88%, HPLC: *t*<sub>R</sub> = 39 min, 33% e.e., [ $\alpha$ ]<sub>D</sub> +1.0 (*c* 2.0, CHCl<sub>3</sub>).

Compound **3b**: White solid, mp 66–70°C (lit.<sup>1a</sup> 65–70°C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.16 (t, 3H, *J* = 7.4 Hz, 4'-CH<sub>3</sub>), 1.71 (m, 2H, 3'-CH<sub>2</sub>), 3.13 (m, 1H, 2'-CH), 3.79 (dd, 1H, *J* = 13.7, 7.0 Hz, NCH(H)), 4.03 (dd, 1H, *J* = 13.7, 8.4 Hz, NC(H)H), 7.76 (m, 2H, ArH), 7.89 (m, 2H, ArH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  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). <sup>1</sup>H NMR spectral data were consistent with the literature.<sup>1a</sup>

**4.6.3. 2-(2'-Cyano-3'-phenylpropyl)phthalimide 3c.** (a) (*E*)-2-(2'-Cyano-3'-phenylprop-2'-enyl)phthalimide **1c** (84 mg), ethyl acetate (7 mL), Pd/CaCO<sub>3</sub> (31 mg) using Method 1 gave **3c**, yield 70% (after chromatography and recrystallisation from ethanol), HPLC: *t*<sub>R</sub> = 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 H<sub>2</sub>, 40°C using Method 2 gave **3c**, yield 78%, HPLC: *t*<sub>R</sub> = 49 min, 3% e.e., [ $\alpha$ ]<sub>D</sub> 0.0 (*c* 2.0, CHCl<sub>3</sub>).

Compound **3c**: White solid, mp 114–116°C (lit.<sup>1a</sup> 114–116°C); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  2.99 (m, 2H, 3'-CH<sub>2</sub>), 3.48 (m, 1H, 2'-CH), 3.84 (dd, 1H, *J* = 13.8, 6.7 Hz, NC(H)H), 4.06 (dd, 1H, *J* = 13.8, 8.6 Hz, NCH(H)), 7.29 (m, 5H, ArH), 7.73 (m, 2H, ArH(Ft)), 7.85 (m, 2H, ArH(Ft)); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  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). <sup>1</sup>H NMR spectral data were consistent with reported data.<sup>1a</sup>

**4.6.4. 2-[3'-(*t*-Butyldimethylsilyl)-2'-cyanopropyl]phthalimide 3d.** (a) (*E*)-2-[3'-(*t*-Butyldimethylsilyl)-2'-cyanoprop-2'-enyl]phthalimide **1d** (100 mg), ethyl acetate (7 mL), Pd/CaCO<sub>3</sub> (30 mg) using Method 1 gave **3d**, yield

93%, HPLC: *t*<sub>R</sub> = 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 H<sub>2</sub>, 40°C using Method 2 gave **3d**, yield 84%, HPLC: *t*<sub>R</sub> = 10 min, 48% e.e., [ $\alpha$ ]<sub>D</sub> –8.3 (*c* 2.0, CHCl<sub>3</sub>).

Compound **3d**: White solid, mp 83.5–86°C; IR:  $\nu$  = 2926, 2854, 2220, 1768, 1708, 1464, 1398, 1377, 1366, 776, 716 cm<sup>–1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.10 (s, 3H, SiCH<sub>3</sub>), 0.16 (s, 3H, SiCH<sub>3</sub>), 0.88 (dd, 1H, *J* = 14.7, 4.9 Hz, SiCH(H)), 0.89 (s, 9H, (CH<sub>3</sub>)<sub>3</sub>C), 1.01 (dd, 1H, *J* = 14.7, 10.7 Hz, SiC(H)H), 3.19 (m, 1H, 2'-CH), 3.71 (dd, 1H, *J* = 13.6, 6.1 Hz, NCH(H)), 4.05 (dd, 1H, *J* = 13.6, 9.6 Hz, NC(H)H), 7.75 (m, 2H, ArH), 7.89 (m, 2H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  –6.2, –5.7 (Si(CH<sub>3</sub>)<sub>2</sub>), 13.7 (C-3'), 16.5 ((CH<sub>3</sub>)<sub>3</sub>C), 26.3 ((CH<sub>3</sub>)<sub>3</sub>C), 27.1 (C-2'), 42.2 (C-1'), 120.9 (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<sup>+</sup>, 2%), 327 (5), 281 (20), 272 (21), (29), 160 (10), 130 (10), 73 (16), 44 (10).

**4.6.5. 2-(2'-Cyano-3'-trimethylsilylpropyl)phthalimide 3e.** (a) (*E*)-2-(2'-Cyano-3'-trimethylsilyl-2'-propenyl)phthalimide **1e** (88 mg), ethyl acetate (7 mL), Pd/CaCO<sub>3</sub> (37 mg) using Method 1 gave **3e**, yield 92% (after chromatography, ethyl acetate:light petroleum, 10:90), HPLC: *t*<sub>R</sub> = 7 and 8 min (Chiralcel OD, flow rate = 1 mL/min, detection at 254 nm, eluent = 80% hexane:20% 2-propanol). (b) Compound **1e** (100 mg), methanol (4 mL), (*R,R*)-EtDuPHOS-Rh(I) (1 mg), 100 psi H<sub>2</sub>, 40°C using Method 2 gave **3e**, yield 93%, HPLC: *t*<sub>R</sub> = 7 min, 10% e.e., [ $\alpha$ ]<sub>D</sub> +2.5 (*c* 2.0, CHCl<sub>3</sub>).

Compound **3e**: Colourless oil; IR:  $\nu$  = 2954, 2241, 1775, 1720, 1468, 1434, 1396, 1356, 1302, 1252, 1191, 1088, 963, 845, 716, 700 cm<sup>–1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.15 (s, 9H, (SiCH<sub>3</sub>)<sub>3</sub>), 0.86 (dd, 1H, *J* = 14.7, 5.1 Hz, SiCH(H)), 1.02 (dd, 1H, *J* = 14.6, 10.7 Hz, SiCH(H)), 3.18 (m, 1H, 2'-CH), 3.71 (dd, 1H, *J* = 13.6, 6.3 Hz, NC(H)H), 4.03 (dd, 1H, *J* = 13.6, 9.2 Hz, NCH(H)), 7.75 (m, 2H, ArH), 7.89 (m, 2H, ArH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  –1.4 (Si(CH<sub>3</sub>)<sub>3</sub>), 17.7 (C-3'), 26.9 (C-2'), 41.9 (C-3'), 120.8 (CN), 123.7 (C-4/7), 131.7 (C-3a/7a), 134.3 (C-5/6), 167.7 (CO); MS (EI): *m/z* 286 (M<sup>+</sup>, 2%), 272 (5), 271 (27), 160 (100), 130 (13), 126 (11), 104 (13), 76 (18), 73 (23), 72 (27), 58 (23), 50 (14); C<sub>15</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>Si (286.41) calcd: C, 62.90; H, 6.33; N, 9.78; found: C, 62.71; H, 6.44; N, 9.71%.

**4.6.6. N-(2'-Cyanopropyl)acetamide 18.** (a) *N*-(2'-Cyanoprop-2'-enyl)acetamide **7** (106 mg), ethyl acetate (7 mL), Pd/CaCO<sub>3</sub> (22 mg) using Method 1 gave **18**, yield 92% (after distillation), HPLC: *t*<sub>R</sub> = 14 and 29 min (Chiralcel OB, flow rate = 1 mL/min, detection at 220 nm, eluent = 90% hexane:10% 2-propanol). (b) Compound **7** (250 mg), methanol (6 mL), (*R,R*)-EtDuPHOS-Rh(I) (2 mg), 60 psi H<sub>2</sub> using Method 2 gave **18**, yield 89% (after chromatography using ethyl acetate:light petroleum:ammonia solution, 2:8:1), HPLC: *t*<sub>R</sub> = 29 min, 64% e.e. (*S*), [ $\alpha$ ]<sub>D</sub> +77.8 (*c* 2.0, CHCl<sub>3</sub>).

Compound **18**: Clear, colourless oil, bp (oven) 114°C/0.5 mm; IR:  $\nu$  = 3293, 3083, 2987, 2942, 2244, 1660,



1556, 1456, 1440, 1376, 1293, 1144, 1115  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.31 (d, 3H,  $J=7.1$  Hz,  $3'\text{-CH}_3$ ), 2.02 (s, 3H,  $\text{OCH}_3$ ), 2.98 (m, 1H,  $2'\text{-CH}$ ), 3.25 (m, 1H,  $\text{NCH(H)}$ ), 3.52 (m, 1H,  $\text{NC(H)H}$ ), 6.78 (s, 1H, NH);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  15.2 (C-3'), 22.8 ( $\text{OCH}_3$ ), 26.4 (C-2'), 42.2 (C-1'), 121.7 (CN), 170.9 (CO); MS (EI):  $m/z$  126 ( $\text{M}^+$ , 5%), 125 (1), 111 (11), 72 (100), 43 (99), 42 (12), 41 (11); HRMS (EI):  $m/z$  calcd for  $\text{C}_6\text{H}_{10}\text{N}_2\text{O}+\text{H}$ : 127.0871; found: 127.0872.

**4.6.7. *t*-Butyl *N*-(2'-cyanopropyl)carbamate 19.** (a) *t*-Butyl *N*-(2'-cyanoprop-2'-enyl)carbamate **8** (160 mg), ethyl acetate (7 mL),  $\text{Pd}/\text{CaCO}_3$  (54 mg) using Method 1 gave **19**, yield 81% (after chromatography using ethyl acetate:light petroleum:ammonia solution, 2:8:1). The enantiomers could not be resolved by HPLC using Chiralcel OD and OB columns. (b) Compound **8** (140 mg), methanol (6 mL), (*R,R*)-EtDuPHOS-Rh(I) (1 mg), 60 psi  $\text{H}_2$  using Method 2 gave **19**, yield 91% (after chromatography as above), HPLC, racemic material,  $[\alpha]_{\text{D}}$  0.0 (*c* 2.0,  $\text{CHCl}_3$ ).

Compound **19**: White solid, mp 79.5–80°C; IR:  $\nu=3342, 2925, 2854, 2243, 1682, 1521, 1460, 1377, 1368, 1282, 1248, 1162, 1146, 984 \text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.29 (d, 3H,  $J=7.1$  Hz,  $3'\text{-CH}_3$ ), 1.44 (s, 9H,  $(\text{CH}_3)_3\text{C}$ ), 2.91 (m, 1H,  $2'\text{-CH}$ ), 3.19 (m, 1H,  $\text{NCH(H)}$ ), 3.37 (m, 1H,  $\text{NC(H)H}$ ), 4.98 (bs, 1H, NH);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  15.2 (C-3'), 27.1 (C-2'), 28.3 ( $(\text{CH}_3)_3\text{C}$ ), 43.6 (C-1'), 80.2 ( $(\text{CH}_3)_3\text{C}$ ), 121.7 (CN), 155.7 (CO); MS (EI):  $m/z$  185 ( $\text{M}^+$ , 1%), 169 (13), 130 (100), 129 (47), 128 (15), 111 (42);  $\text{C}_6\text{H}_{16}\text{N}_2\text{O}_2$  (184.24) calcd: C, 58.67; H, 8.75; N, 15.21; found: C, 58.49; H, 8.62; N, 15.09%.

**4.6.8. Methyl 2-methyl-3-phthalimidopropanoate 17a.** (a) Methyl 2-(phthalimidomethyl)prop-2-enoate **9a** (72 mg), ethyl acetate (7 mL),  $\text{Pd}/\text{CaCO}_3$  (32 mg) using Method 1 gave **17a**, yield 91%; HPLC:  $t_{\text{R}}=51$  and 59 min (Chiralcel OJ, flow rate=1 mL/min, detection at 254 nm, eluent=99% hexane:1% 2-propanol). (b) Compound **9a** (70 mg), methanol (4 mL), (*R,R*)-EtDuPHOS-Rh(I) (1 mg), 50 psi  $\text{H}_2$ , 40 h using Method 2 gave **17a**, yield 93%, HPLC:  $t_{\text{R}}=59$  min, 12% e.e. (*S*),  $[\alpha]_{\text{D}}+6.3$  (*c* 1.0,  $\text{CHCl}_3$ ). (c) Compound **9a** (52 mg), methanol (4 mL), (*S*)-BINAP-Ru(II) (1 mg), 100 psi  $\text{H}_2$ , 40 h using Method 2 gave **17a**, yield 92%, HPLC:  $t_{\text{R}}=51$  min, 80% e.e. (*R*),  $[\alpha]_{\text{D}}-16.9$  (*c* 1.0,  $\text{CHCl}_3$ ). (d) Compound **9a** (10 mg), methanol (2 mL), (*S*)-BINAP-Ru(II) (1 mg), 50 psi  $\text{H}_2$ , 40 h gave **17a**, yield 91%, HPLC:  $t_{\text{R}}=51$  min, 84% e.e. (*R*),  $[\alpha]_{\text{D}}-17.2$  (*c* 0.95,  $\text{CHCl}_3$ ).

Compound **17a**: White solid, mp 86–87°C; IR:  $\nu=2921, 2853, 1775, 1731, 1707, 1463, 1398, 1376, 1358, 1322, 1212, 1190, 1065, 1033, 911, 791 \text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.21 (d, 3H,  $J=7.1$  Hz,  $\text{CH}_3$ ), 2.98 (sept., 1H,  $J=7.1$  Hz,  $2'\text{-CH}$ ), 3.66 (s, 3H,  $\text{OCH}_3$ ), 3.78 (dd, 1H,  $J=13.8, 6.8$  Hz,  $\text{NC(H)H}$ ), 3.97 (dd, 1H,  $J=13.8, 7.6$  Hz,  $\text{NCH(H)}$ ), 7.72 (m, 2H, ArH), 7.85 (m, 2H, ArH);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  14.7 ( $\text{CH}_3$ ), 38.5 (C-2), 40.6 (C-3), 52.0

( $\text{OCH}_3$ ), 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 ( $\text{M}^+$ , 3%), 217 (1), 188 (13), 187 (40), 161 (11), 160 (100);  $\text{C}_{13}\text{H}_{13}\text{NO}_4$  (247.25) calcd: 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-enoate **9b** (20 mg), ethyl acetate (3 mL),  $\text{Pd}/\text{CaCO}_3$  (5 mg) using Method 1 gave **17b**, yield 89%, HPLC:  $t_{\text{R}}=50$  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  $\text{H}_2$ , 100°C, 40 h using Method 2 gave **17b**, yield 91%, HPLC:  $t_{\text{R}}=50$  min, 10% e.e.,  $[\alpha]_{\text{D}}$  0.0 (*c* 1.0,  $\text{CHCl}_3$ ).

Compound **17b**: White solid, mp 81–83°C, IR:  $\nu=2926, 2856, 1772, 1724, 1463, 1396, 1377, 1356, 1176, 1045, 722 \text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.96 (t, 3H,  $J=7.4$  Hz, 4- $\text{CH}_3$ ), 1.64 (m, 2H, 3- $\text{CH}_2$ ), 2.82 (m, 1H, 2-CH), 3.66 (s, 3H,  $\text{OCH}_3$ ), 3.81 (dd, 1H,  $J=13.8, 6.2$  Hz,  $\text{NC(H)H}$ ), 3.95 (dd, 1H,  $J=13.8, 8.0$  Hz,  $\text{NCH(H)}$ ), 7.71 (m, 2H, ArH), 7.84 (m, 2H, ArH);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  11.4 (C-4), 22.9 (C-3), 39.3 ( $\text{NCH}_2$ ), 46.0 (C-2), 51.9 ( $\text{OCH}_3$ ), 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 ( $\text{M}^+$ , <1%), 230 (4), 201 (50), 186 (11), 160 (100), 133 (10). HRMS (EI):  $m/z$  calcd for  $\text{C}_{14}\text{H}_{15}\text{NO}_4$ : 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,<sup>20</sup> **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  $\text{NH}_4\text{Cl}$  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-propyl)phthalimide **3a** (sample having  $[\alpha]_{\text{D}}+8.3$ , 14% e.e., see Section 4.6.1.b) (60 mg) gave **12**, yield 58%;  $[\alpha]_{\text{D}}$  (corrected for chemical conversion) +19.0 (*c* 0.42,  $\text{D}_2\text{O}$ ), (*S*)-enantiomer. (b) *N*-(2'-Cyano-2'-propenyl)acetamide **18** (sample having  $[\alpha]_{\text{D}}+77.8$ , 64% e.e., see Section 4.6.6) (63 mg) gave **12**, yield 88%,  $[\alpha]_{\text{D}}+7.6$  (*c* 0.42,  $\text{H}_2\text{O}$ ), (*S*)-enantiomer.

**4.7.2. (*R*)- $\alpha$ -Methyl- $\beta$ -alanine 12.** Methyl 2-methyl-3-phthalimidopropanoate **17a** (sample having  $[\alpha]_{\text{D}}-16.9$ , 80% e.e., see Section 4.6.8) (49 mg) gave **12**, yield 90%,  $[\alpha]_{\text{D}}$  (corrected for chemical conversion) -8.2 (*c* 0.42,  $\text{D}_2\text{O}$ ), (*R*)-enantiomer.

Compound **12**:  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}$ )  $\delta$  1.18 (d, 3H,  $J=7.3$  Hz,  $\text{CH}_3$ ), 2.64 (m, 1H, 2-CH), 3.03 (dd, 1H,  $J=12.9$ , 5.3 Hz, NCH(H)), 3.11 (dd, 1H,  $J=12.9$ , 8.4 Hz, NC(H)H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{D}_2\text{O}$ )  $\delta$  15.0 ( $\text{CH}_3$ ), 38.8 (C-2), 42.3 (C-3), 180.8 (CO); MS (EI):  $m/z$  103 ( $\text{M}^+$ , 8%), 89 (86), 87 (100), 85 (11), 83 (17), 78 (11), 55 (30), 44 (12), 43 (40) (lit.<sup>9</sup>  $[\alpha]_{\text{D}} -14.0$  ( $c$  0.42,  $\text{D}_2\text{O}$ ) for the (*R*)-enantiomer).

#### 4.8. Preparation of *N*-benzoyl derivatives of **12**

**4.8.1. 3-(Benzoylamino)-2-methylpropanoic acid.** A solution of  $\alpha$ -methyl- $\beta$ -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) to remove base soluble material, acidified with HCl (2 M) and the aqueous solution extracted with ethyl acetate (3 $\times$ 15 mL). The organic extracts were washed with brine (15 mL), dried ( $\text{MgSO}_4$ ), 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:  $\nu=3448$ , 3054, 2986, 1708, 1663, 1604, 1579, 1522, 1488, 1465, 1422, 1154  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  1.27 (d, 3H,  $J=7.2$  Hz,  $\text{CH}_3$ ), 2.85 (m, 1H, 2-CH), 3.51 (m, 1H, NCH(H)), 3.74 (m, 1H, NC(H)H), 6.95 (bs, 1H, NH), 7.45 (m, 3H, ArH), 7.75 (m, 2H, ArH);  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  14.9 ( $\text{CH}_3$ ), 39.6 (C-2), 42.1 (C-3), 127.1, 128.7, 131.8 (ArCH), 134.2 (ArC), 168.2 (COAr), 180.6 ( $\text{CO}_2\text{H}$ ); MS (EI):  $m/z$  207 ( $\text{M}^+$ , 3%), 189 (2), 161 (15), 122 (30), 105 (62). HRMS (EI):  $m/z$  calcd for  $\text{C}_{11}\text{H}_{13}\text{NO}_3$ : 207.0895; found: 207.0901.

**4.8.2. Ethyl 3-(Benzoylamino)-2-methylpropanoate **14**.** Method A: Ethyl iodide (28  $\mu\text{L}$ , 0.35 mmol) was added to a solution of racemic 3-(benzoylamino)-2-methylpropanoic acid (prepared from racemic  $\alpha$ -methyl- $\beta$ -alanine) (50 mg, 0.29 mmol) and freshly distilled 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) (52  $\mu\text{L}$ , 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 $\times$ 10 mL), dried over  $\text{MgSO}_4$ , filtered and the solvent removed in vacuo to give a yellow oil. Flash chromatography (ethyl acetate:light petroleum, 30:70) gave the ester **14**, yield 72%, HPLC:  $t_{\text{R}}=59$  and 68 min (Chiralcel OJ, flow rate=1 mL/min, detection at 254 nm, eluent=99.5% hexane:0.5% 2-propanol).

Method B: 3-(Benzoylamino)-2-methylpropanoic acid (50 mg, 0.24 mmol) was dissolved in dry ethanol (3 mL) and the solution cooled to  $0^\circ\text{C}$  before the slow addition of chlorotriethylsilane (61  $\mu\text{L}$ , 0.36 mmol). The resulting solution was stirred at  $0^\circ\text{C}$  for 1.5 h and at ambient temperature for a further 6 h. Evaporation afforded the ester **14** which was purified as above (yield 100%).

(a) (*S*)- $\alpha$ -Methyl- $\beta$ -alanine **12** (prepared as described in Section 4.7.1 from a sample of nitrile **3a** having an  $[\alpha]_{\text{D}} +8.3$ ) (120 mg) using Method A gave **14**, yield 78%,

HPLC:  $t_{\text{R}}=59$  min, 11% e.e., (*S*)-enantiomer,  $[\alpha]_{\text{D}} +3.1$  ( $c$  1.0,  $\text{CHCl}_3$ ). (b) (*S*)- $\alpha$ -Methyl- $\beta$ -alanine **12** (prepared as described in Section 4.7.1 from a sample of nitrile **3a** having an  $[\alpha]_{\text{D}} +8.3$ ) (50 mg) using Method B gave **14**, yield 100%,  $[\alpha]_{\text{D}} +3.4$  ( $c$  1.0,  $\text{CHCl}_3$ ).

Compound **14**: Yellow viscous oil; IR:  $\nu=3331$ , 2981, 2938, 1732, 1644, 1603, 1580, 1538, 1490, 1463, 1380, 1310, 1258, 1190, 1135, 1096, 1076, 1024, 713, 695  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  1.24 (d, 3H,  $J=7.3$  Hz,  $\text{CH}_3$ ), 1.27 (t, 3H,  $J=7.2$  Hz,  $\text{CH}_2\text{CH}_3$ ), 2.81 (m, 1H, 2-CH), 3.51 (m, 1H, NCH(H)), 3.71 (m, 1H, NC(H)H), 4.17 (q, 2H,  $J=7.1$  Hz, 2H,  $\text{CH}_2\text{CH}_3$ ), 6.91 (bs, 1H, NH), 7.46 (m, 3H, ArH), 7.77 (m, 2H, ArH);  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  14.3, 15.0 ( $\text{CH}_3$ ,  $\text{CH}_2\text{CH}_3$ ), 39.6 (C-2), 42.1 (C-3), 60.9 ( $\text{CH}_2\text{CH}_3$ ), 127.0, 128.6, 131.5 (ArCH), 134.5 (ArC), 167.5 (COPh), 175.9 ( $\text{CO}_2$ ); MS (EI):  $m/z$  235 ( $\text{M}^+$ , 10%), 190 (17), 134 (10), 105 (100), 75 (10), 76 (13); HRMS (EI):  $m/z$  calcd for  $\text{C}_{13}\text{H}_{17}\text{NO}_3$ : 235.1208; found: 235.1205.

#### 4.9. 3-[(9*H*-Fluoren-9-ylmethoxy)carbonylamino]-2-methylpropanoic acid **13**

$\alpha$ -Methyl- $\beta$ -alanine hydrochloride **11** (0.92 g, 8.96 mmol) and sodium carbonate (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-fluorenylmethoxycarbonyloxy)succinimide (Fmoc-OSu) (3.02 g, 8.96 mmol) in acetone (15 mL) was added dropwise. The mixture was stirred at  $4^\circ\text{C}$  for 20 min and at ambient temperature for 4 h, diluted with water (80 mL) and washed with ethyl acetate (30 mL). The aqueous layer was acidified to pH 3–4 with concentrated HCl and extracted with ethyl acetate (3 $\times$ 30 mL). The organic extracts were combined, washed with water (2 $\times$ 30 mL), brine (20 mL), dried over  $\text{MgSO}_4$ , 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  $\alpha$ -methyl- $\beta$ -alanine **12** (sample having an  $[\alpha]_{\text{D}} +19.0$ , see Section 4.7.1.a) (100 mg) with Fmoc-Osu (330 mg) as described above gave **13**, yield 35%;  $[\alpha]_{\text{D}} +25.5$  ( $c$  1.0,  $\text{CH}_2\text{Cl}_2$ ) (*S*)-enantiomer (lit.<sup>12</sup>  $[\alpha]_{\text{D}} +9$  ( $c$  1.0,  $\text{CH}_2\text{Cl}_2$ ) (*S*)-enantiomer. (b) An identical reaction of a freshly prepared sample of **12** gave **13**, yield 33%;  $[\alpha]_{\text{D}} +2.5$  ( $c$  1.0,  $\text{CH}_2\text{Cl}_2$ ).

Compound **13**: White solid; mp  $165.5$ – $168^\circ\text{C}$  (lit.<sup>12</sup>  $165.5$ – $168^\circ\text{C}$ ); IR:  $\nu=3337$ , 2924, 2854, 1692, 1544, 1460, 1377, 1273, 1221, 1159, 1006, 758, 742, 734  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  0.99 (m, 3H,  $\text{CH}_3$ ), 2.60 (sept., 1H,  $J=7.0$  Hz, 2-CH), 3.16 (dd, 1H,  $J=13.5$ , 6.4 Hz, NCH(H)), 3.33 (dd, 1H,  $J=13.6$ , 6.5 Hz, NC(H)H), 4.16 (m, 1H, 9'-CH), 4.30 (m, 2H,  $\text{OCH}_2$ ), 4.47 (bs, 1H, NH);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  12.7 ( $\text{CH}_3$ ), 38.6 (C-9'), 42.2 (C-3), 46.1 (C-2), 65.3 ( $\text{OCH}_2$ ), 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 ( $\text{CO}_2\text{H}$ ); MS (EI):  $m/z$  325 ( $\text{M}^+$ , <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'-<sup>2</sup>H<sub>1</sub>,3'-<sup>2</sup>H<sub>1</sub>)-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 20°C gave **16a** as a white solid after chromatography, yield 81%; IR:  $\nu$ =2923, 2854, 2243, 1777, 1715, 1464, 1435, 1394, 1378, 1354, 973, 720 cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.37 (bs, 2H, CH<sub>2</sub>D), 3.75 (d, 1H,  $J$ =13.7 Hz, NCH(H)), 4.00 (d, 1H,  $J$ =13.7 Hz, NC(H)H), 7.76 (m, 2H, ArH), 7.88 (m, 2H, ArH); <sup>2</sup>H NMR (61.4 MHz, CDCl<sub>3</sub>)  $\delta$  1.29 (bs, 1D, 3'-D), 3.11 (bs, 1D, 2'-D); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  15.2 (t,  $J$ =20.0 Hz, C-3'), 24.9 (t,  $J$ =21.1 Hz, C-2'), 40.1 (C-1'), 120.4 (CN), 123.7 (C-4/7), 131.7 (C-3a/7a), 134.4 (C-5/6), 167.7 (CO); HRMS (EI)  $m/z$  calcd for C<sub>12</sub>H<sub>8</sub>D<sub>2</sub>N<sub>2</sub>O<sub>2</sub>: 216.0866; found: 216.0870;  $[\alpha]_D$  +8.5 (c 2.0, CHCl<sub>3</sub>).

**4.10.2. (2'-<sup>2</sup>H<sub>1</sub>,3'-<sup>2</sup>H<sub>1</sub>)-2-(2'-Cyanobutyl)phthalimide 16b.** Reaction of 2-(2'-cyano-2'-butenyl)phthalimide **1b** (100 mg, 0.43 mmol), methanol (5 mL) and (R,R)-EtDuPHOS-Rh(I) (1 mg) with deuterium (100 psi) at 40°C gave **16b** as a white solid after chromatography, yield 81%; IR:  $\nu$ =2923, 2854, 2243, 1773, 1721, 1463, 1438, 1396, 1376, 1352, 989, 722 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  1.15 (d, 3H,  $J$ =7.4 Hz, 4'-CH<sub>3</sub>), 1.70 (m, 1H, 3'-CH), 3.79 (d, 1H,  $J$ =13.7 Hz, NCH(H)), 4.02 (d, 1H,  $J$ =13.7 Hz, NC(H)H), 7.76 (m, 2H, ArH), 7.88 (m, 2H, ArH); <sup>2</sup>H NMR (61.4 MHz, CDCl<sub>3</sub>)  $\delta$  1.59 (bs, 1D, 3'-D), 3.02 (bs, 1D, 2'-D); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  11.1 (C-4'), 22.7 (t,  $J$ =20.1 Hz, C-3'), 32.4 (t,  $J$ =21.0 Hz, C-2'), 38.6 (C-1'), 119.5 (CN), 123.7 (C-4/7), 131.7 (C-3a/7a), 134.4 (C-5/6), 167.7 (CO); HRMS (EI)  $m/z$  calcd for C<sub>13</sub>H<sub>10</sub>D<sub>2</sub>N<sub>2</sub>O<sub>2</sub>: 230.1022; found: 230.1026;  $[\alpha]_D$  +1.2 (c 2.0, CHCl<sub>3</sub>).

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