

Enantiospecific alkylations of alanine

Francisco Alonso,^a Stephen G. Davies,^{*a} Almut S. Elend^a and Jane L. Haggitt^b

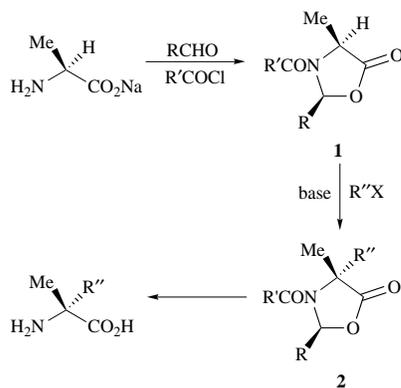
^a The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford, UK OX1 3QY

^b Chemical Crystallography Laboratory, University of Oxford, South Parks Road, Oxford, UK OX1 3PD

Reaction of ferrocenecarbaldehyde **3** with sodium (*S*)-alaninate followed by pivaloyl chloride generates (2*S*,4*S*)-2-ferrocenyl-3-pivaloyl-4-methyl-1,3-oxazolidin-5-one **5** (>98% de). Compound **5** undergoes stereospecific 4-alkylation with complete retention of configuration on treatment sequentially with lithium diisopropylamide and an appropriate alkyl bromide {benzyl bromide, allyl bromide, crotyl [(*E*)-but-2-enyl] bromide, α -bromo-*o*-xylene, cinnamyl bromide, 2-(bromomethyl)naphthalene, 1-(*tert*-butoxycarbonyl)-3-(bromomethyl)indole and bromoacetonitrile} to generate the corresponding (2*S*,4*R*)-2-ferrocenyl-3-pivaloyl-4-alkyl-4-methyl-1,3-oxazolidin-5-ones **7a–h**. Hydrolysis of (2*S*,4*R*)-**7a–h** on Amberlyst-15 generates the free (*R*)- α -methyl- α -amino acids (*R*)-**8a–h**.

Introduction

In recent years α -substituted- α -amino acids have received much attention due to their important and diverse biological functions.¹ Often enantiomers of the same α -amino acid exhibit different biological activities. Therefore much effort has gone into developing practical methodologies for the asymmetric synthesis of homochiral α -substituted- α -amino acids.² The most famous among these methodologies are Schöllkopf's bis-lactim ether,³ Seebach's imidazolidinones and oxazolidinones⁴ and Williams's diphenyloxazinones.⁵ The method most commonly used to access α -methyl- α -amino acids is probably Seebach's oxazolidinone methodology or a variant thereof (Scheme 1).⁶



Scheme 1

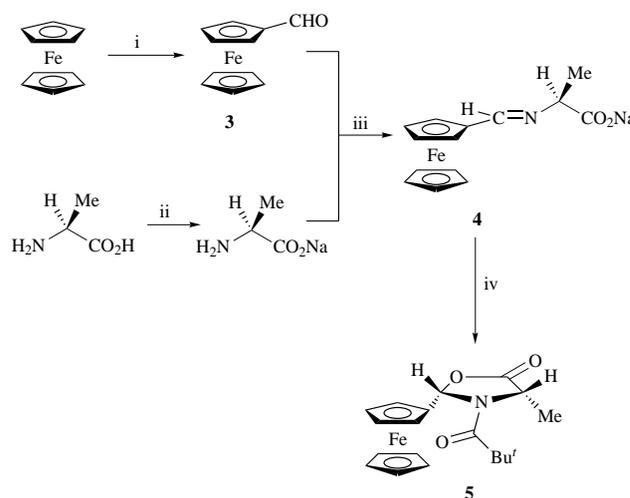
The practical limitations of this elegant strategy, however, curtail its usefulness. Firstly, the formation of the initial *cis*-1,3-oxazolidin-5-ones **1** and their subsequent *trans*-alkylation to form oxazolidinones **2** are not completely stereoselective, therefore rendering purification by crystallisation or chromatography necessary at both stages. Secondly, the *trans*-alkylated 1,3-oxazolidin-5-ones **2** are relatively stable species requiring harsh hydrolysis conditions to liberate the product α -methyl- α -amino acids, conditions which are not compatible with acid sensitive substituents.

We proposed to eliminate the above problems by using ferrocenecarbaldehyde and pivaloyl chloride to form the alanine derived oxazolidinone. Introducing two bulky groups, ferrocene and pivaloyl, onto the oxazolidinone ring promised a good chance of improving the stereoselectivities of both the ring formation and the alkylation step. Furthermore, the elec-

tronic properties of ferrocene, due to the fact that it contains the transition metal iron bearing lone pairs, gave us good reason to believe that ferrocene would facilitate the hydrolysis of the alkylated oxazolidinone **2** via neighbouring group participation. Part of this work has been previously communicated.⁷

Results and discussion

Commercially available ferrocenecarbaldehyde **3** was prepared more cheaply from ferrocene using *N*-methylformanilide and phosphorus oxychloride in 87% yield.⁸ Treatment of ferrocenecarbaldehyde **3** with sodium (*S*)-alaninate, derived from (*S*)-L-alanine, in absolute ethanol generated in 95% yield the imine (*S*)-**4**, which was cyclised with pivaloyl chloride in dichloromethane to give the expected thermodynamically more stable *cis*-1,3-oxazolidin-5-one diastereoisomer (2*S*,4*S*)-**5** in 95% yield (Scheme 2).



Scheme 2 Reagents and conditions: i, 3 equiv. PhMeNCHO, 2 equiv. POCl₃, 3 d, RT, 87% yield; ii, aq. NaOH, quantitative yield; iii, absolute ethanol, 4 Å molecular sieves, 5 h, RT, 95% yield; iv, Bu'COCl, DCM, 4 Å molecular sieves, overnight, -18 °C to RT, 95% yield, >98% de

The 1,3-oxazolidin-5-one **5** was shown to be diastereoisomerically pure (>98% de) by ¹H and ¹³C NMR spectroscopic analysis and shown to be homochiral (>98% ee) by use of the chiral shift reagent (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoro-

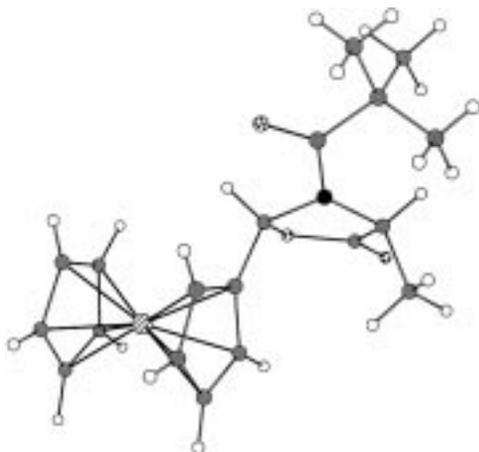
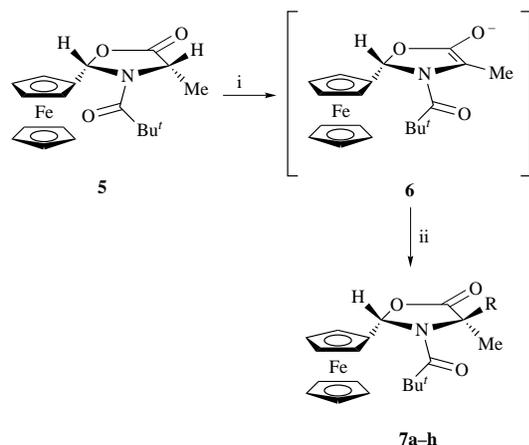


Fig. 1 Single crystal X-ray structure of racemic (2*RS*,4*RS*)-**5** [(2*S*,4*S*)-**5** is depicted]

ethanol,⁹ thus demonstrating that the original stereochemical integrity derived from (*S*)-L-alanine had not been compromised in the formation of (2*S*,4*S*)-**5**. The *cis* relationship of the ring substituents was assigned by NOE experiments and unambiguously confirmed by a single crystal X-ray structure analysis on a sample from the racemic series (Fig. 1). The absolute configuration of (2*S*,4*S*)-**5** follows from that of the starting material (*S*)-L-alanine.

Treatment of (2*S*,4*S*)-**5** with lithium diisopropylamide (LDA) to generate the enolate **6** and subsequent quenching with benzyl bromide generated (2*S*,4*R*)-2-ferrocenyl-3-pivaloyl-4-benzyl-4-methyl-1,3-oxazolidin-5-one **7a** as a single diastereoisomer by ¹H and ¹³C NMR spectroscopic analysis (Scheme 3).



Scheme 3 Reagents and conditions: i, LDA, THF, $-78\text{ }^{\circ}\text{C}$; ii, RBr, THF, $-78\text{ }^{\circ}\text{C}$ up to RT, overnight, 71–95% yield, 92–>98% de

The 1,3-oxazolidin-5-one **7a** was shown to be homochiral (>98% ee) by use of the chiral shift reagent (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol,⁹ thus demonstrating that the original (2*S*) stereochemical integrity deriving from (2*S*,4*S*)-**5** had not been compromised in the formation of (2*S*,4*R*)-**7a**. The *cis* relationship of the ferrocenyl and methyl substituents was assigned by NOE experiments and unambiguously confirmed by a single crystal X-ray structure analysis of (2*RS*,4*SR*)-**7a** from the racemic series (Fig. 2). The absolute configuration of (2*S*,4*R*)-**7a** follows from that of (2*S*,4*S*)-**5**. The alkylation of (2*S*,4*S*)-**5** to (2*S*,4*R*)-**7a** thus proceeded completely stereospecifically with retention of configuration.

Similar sequential treatment of (2*S*,4*S*)-**5** with LDA and a variety of alkyl bromides generated the corresponding (2*S*,4*R*)-1,3-oxazolidin-5-ones **7(b–h)** (Scheme 3). Yields and diastereomeric excesses for these alkylation reactions are given in Table 1.

The X-ray structures of (2*S*,4*S*)-**5** (Fig. 1) and (2*S*,4*R*)-**7a**

Table 1 Yields and diastereoselectivities for the alkylations of (2*S*,4*S*)-**5** to (2*S*,4*R*)-**7(a–h)**

Entry	Electrophile	Product	Yield (%) ^a	De (%) ^b
1	benzyl bromide	7a	90	>98
2	allyl bromide	7b	78	>96
3	crotyl bromide	7c	71	92
4	α -bromo- <i>o</i> -xylene	7d	89	96
5	cinnamyl bromide	7e	94	>98
6	2-(bromomethyl)naphthalene	7f	95	>98
7	1-(<i>tert</i> -butoxycarbonyl)-3-(bromomethyl)indole	7g	82	96
8	bromoacetonitrile	7h	86	92

^a Isolated yield. ^b Des determined by ¹H NMR spectroscopic analysis of the crude products.



Fig. 2 Single crystal X-ray structure of racemic (2*RS*,4*SR*)-**7a** [(2*S*,4*R*)-**7a** is depicted]

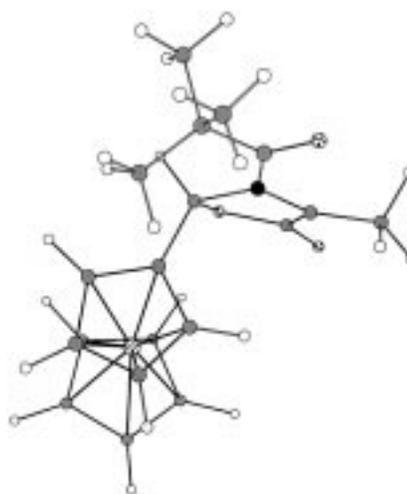


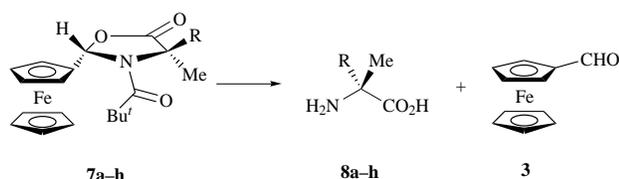
Fig. 3 Computer generated minimum energy conformation for enolate **6**

(Fig. 2) show the pivaloyl oxygen to be *anti*-periplanar to C-4 in **5** but *syn*-periplanar to C-4 in **7a**. Computer aided molecular modelling¹⁰ confirmed in each case that these conformations were by far the most stable. A computer generated model of the intermediate enolate **6** (Fig. 3) based on the crystal structures of **5** and **7a** suggests that by far the most stable conformation in this case has the pivaloyl oxygen *syn*-periplanar to C-4.

The origin of the high diastereoselectivities observed in the conversions of **5** to **7** can therefore be rationalised by envisaging the following mechanism. In the starting 1,3-oxazolidin-5-one **5** the pivaloyl *tert*-butyl group adopts a position distal from the large ferrocenyl substituent and proximal to the C-4 hydrogen

to minimise steric interactions. Upon deprotonation C-4 becomes sp^2 hybridised and the methyl substituent moves into the plane of the oxazolidinone ring, thereby forcing the pivaloyl group to rotate, so that in the enolate the pivaloyl *tert*-butyl group is proximal to the ferrocenyl substituent to avoid eclipsing interactions with the C-4 methyl group. To minimise steric interactions the ferrocenyl substituent rotates to a position underneath the oxazolidinone ring, thereby efficiently shielding the proximal face of the oxazolidinone ring and forcing any incoming electrophile to attack the enolate from the distal face leading to essentially exclusive *trans*-alkylation. In contrast to the preferred conformation of the pivaloyl moiety in **5**, in the product 4-benzyl derivative **7a** the pivaloyl *tert*-butyl group prefers to be adjacent to the ferrocenyl substituent rather than close to the now quaternary centre at C-4 again to minimise steric interactions.

Hydrolysis of (2*S*,4*R*)-**7a–h** on Amberlyst-15 released ferrocenecarbaldehyde **3** (80–95%), pivalic acid and the free α -methyl- α -amino acid (*R*)-**8a–h** (71–95%) (Scheme 4).



Scheme 4 Reagents and conditions: Amberlyst-15, acetone–H₂O (9:1), RT, overnight (71–95%)

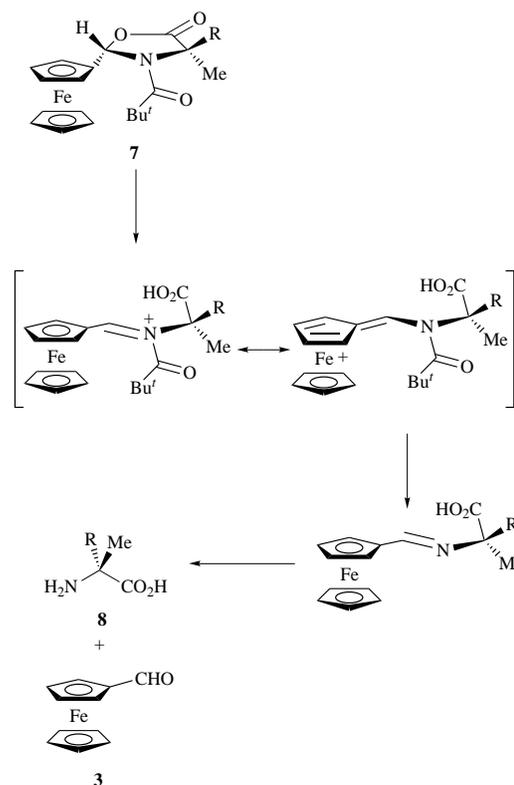
The amino acid (*R*)-**8a** was shown to be homochiral after derivatisation to the corresponding Mosher's amide¹¹ and ¹H and ¹⁹F NMR spectroscopic analysis. The absolute configuration followed from that of (2*S*,4*R*)-**7a** and was confirmed by comparison of the sign of the specific rotation $[\alpha]_{578}^{25} +17.0$ (*c* 0.1, MeOH) with those in the literature $[\alpha]_{578}^{24} +20.0$ (*c* 0.1, MeOH)^{4b} and $[\alpha]_{578}^{25} +19.0$ (*c* 0.1, MeOH).^{6b}

The ease with which the oxazolidinone ring is cleaved can be rationalised by invoking the known propensity of the ferrocenyl group to act as a neighbouring group (Scheme 5).¹² Under the mild acidic conditions on Amberlyst-15 the oxazolidinone ring of **7** opens up easily with neighbouring group participation from the ferrocenyl moiety to give the corresponding stabilised iminium ion. The pivaloyl group is then rapidly hydrolysed from the iminium ion to generate the corresponding imine, which in turn is hydrolysed to release the product α -methyl- α -amino acid and the recyclable starting material ferrocenecarbaldehyde **3**. Without this neighbouring group participation other hydrolysis manifolds would take over which do not proceed *via* the acyliminium ion and *N*-pivaloyl- α -methyl- α -amino acid derivatives would be observed. This is the case for the hydrolysis of **7f** where in air 2-pivaloylamino-2-methyl-3-naphthalen-2-ylpropionic acid is obtained as a byproduct presumably due to oxidation of the ferrocenyl to the ferrocenium ion preventing neighbouring group participation: this byproduct is not observed when the hydrolysis is performed under an inert atmosphere.

In conclusion, a versatile auxiliary has been developed for the asymmetric synthesis of α -methyl- α -amino acids stereospecifically from alanine based on a self-reproduction of chirality strategy.

Experimental

Melting points (mp) were obtained using a ThermogalenTM III or Griffin Gallenkamp melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter with a thermally jacketted 10 cm cell at approximately 20 °C. Concentrations (*c*) are given in g/100 ml and $[\alpha]$ values are given in units of 10^{-1} deg cm² g⁻¹. Infrared



Scheme 5

(IR) spectra were recorded as KBr discs on a Perkin-Elmer 1750 Fourier Transform spectrometer. Absorptions are reported in wavenumbers (cm^{-1}). The following abbreviations are used: w, weak; m, medium; s, strong and br, broad. Proton magnetic resonance spectra (¹H NMR) were recorded at 200 MHz on a Varian Gemini 200 or a Bruker AC200 spectrometer, at 300 MHz on a Bruker WH300, at 400 MHz on a Bruker AC400 and at 500 MHz on a Bruker AM500 spectrometer. For ¹H NMR recorded in CDCl₃, MeOD, C₆D₅CD₃ and D₂O chemical shifts (δ_H) are quoted in parts per million (ppm) and are referenced to the residual solvent peak. The following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and br, broad. Coupling constants (*J*) were recorded in Hz to the nearest 0.5 Hz. Carbon magnetic resonance spectra (¹³C NMR) were recorded at 50.3 MHz on a Varian Gemini 200 or Bruker AC200 spectrometer, at 100.6 MHz on a Bruker AC400 spectrometer and at 125.7 MHz on a Bruker AMX500 spectrometer using DEPT editing. Chemical shifts (δ_C) are quoted in ppm and referenced to CDCl₃, MeOD and C₆D₅CD₃ unless otherwise stated. Spectra recorded in D₂O are referenced to internal 1,4-dioxane. Diastereoisomeric excesses were determined by peak integration of the crude reaction products' ¹H and ¹³C NMR spectra. Cp and Cp' refer to the substituted and unsubstituted cyclopentadiene rings, respectively. Low resolution mass spectra (*m/z*) were recorded on a VG Micromass ZAB 1F, a VG Masslab 20-250, a GCMS Trio 1, a VG BIO Q or an APCI Platform spectrometer, with only molecular ions (*M*⁺), fragments from molecular ions and major peaks being reported. Microanalyses were performed by Mrs V. Lamburn or Mr R. Prior, Dyson Perrins Laboratory, University of Oxford. Column chromatography was performed on silicagel (Kiesel 60), Amberlyst-15 (wet) or Dowex (50WX8-200) resin. Anhydrous dichloromethane (DCM) was obtained by distillation from calcium hydride under nitrogen. Anhydrous Et₂O and anhydrous THF were obtained by distillation from sodium–benzophenone ketyl under nitrogen. Petroleum refers to light petroleum (bp 40–60 °C), redistilled before use.

Unless otherwise stated all reactions were performed and worked-up under a nitrogen atmosphere.

Ferrocenecarbaldehyde 3

The method was modified from that of Pauson and co-workers.⁸ A reaction mixture of *N*-methylformanilide (49.8 ml, 403 mmol, 3 equiv.) and phosphorus oxychloride (25.1 ml, 269 mmol, 2 equiv.) was mechanically stirred at room temperature for 30 min. Ferrocene (25.0 g, 134 mmol, 1 equiv.) was added and the dark purple reaction mixture was mechanically stirred at room temperature for 3 d. The reaction was quenched by pouring it onto ice. After 2 h the product was extracted by washing the water layer with Et₂O (5 × 400 ml). The combined Et₂O layers were dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO₂; petroleum–Et₂O, 7:3 to 5:5) and subsequent recrystallisation from hot petroleum to yield *ferrocenecarbaldehyde* **3** as red–orange crystals (25.0 g, 87%); δ_H(200 MHz; CDCl₃) 4.92 (5H, s, Cp'), 4.63–4.61 and 4.82–4.80 (2 × 2H, 2 × m, Cp) and 9.97 (1H, s, CHO).

(*S*)-Sodium 2-[(ferrocenylmethylidene)amino]propanoate 4

Aqueous NaOH (0.448 g, 11.2 mmol in 11 ml of water) was added to (*S*)-alanine (1.0 g, 11.22 mmol) and stirred for several minutes at room temperature. The solution was concentrated *in vacuo* and the residue dried at 60 °C under high vacuum overnight. 4 Å Molecular sieves, ferrocenecarbaldehyde **3** (2.52 g, 11.78 mmol) and absolute ethanol (50 ml) were added to the alaninate sodium salt and the mixture stirred for 5 h; the course of the reaction could be followed by IR spectroscopy. The molecular sieves were separated by filtration, the filtrate was concentrated on the vacuum line and a red solid was obtained. Pentane (50 ml) was added and stirred until a suspension was formed, which was filtered through a sinter. The residue was washed with more pentane and dried under vacuum to yield ferrocenecarbaldehyde sodium (*S*)-alaninate imine **4** as a yellow–orange solid (3.28 g, 95%); mp 185–188 °C; [α]_D²⁵ –36.1 (*c* 0.16, MeOH); ν_{max}(FT IR, KBr disc)/cm^{–1} 2969m and 2872m (C–H), 1641s (C=O), 1587s (C=N) and 1397m; δ_H(200 MHz; CD₃OD) 1.41 (3H, d, *J* 7, CHCH₃), 3.86 (1H, q, *J* 7, CHCH₃), 4.21 (5H, s, Cp'), 4.29–4.99 (4H, m, Cp) and 8.17 (1H, br s, CH=N); δ_C(50.3 MHz; CD₃OD) 20.47 (CHCH₃), 69.27, 69.78, 71.44 and 71.81 (9 × CH in Cp and Cp' and CHCH₃) and 80.37 (quaternary C in Cp); *m/z* (FAB⁺) 330 [(M + Na)⁺, 100%], 308 [(M + H)⁺, 97], 286 [(M – Na + 2H)⁺, 53] and 137 (56). The imine rapidly undergoes hydrolysis on silica or in the presence of water.

(2*S*,4*S*)-2-Ferrocenyl-3-pivaloyl-4-methyl-1,3-oxazolidin-5-one 5

4 Å Molecular sieves and DCM (90 ml) were added to the imine **4** (3 g, 9.77 mmol) and the mixture was cooled to –18 °C. Then pivaloyl chloride (1.21 ml, 9.77 mmol) distilled from calcium chloride dissolved in DCM (10 ml) was added dropwise. The reaction mixture was stirred overnight while warming to room temperature. Then the reaction mixture was filtered and the filtrate concentrated on a vacuum line; it is very important not to heat the solution, otherwise racemisation occurs. Several portions of Et₂O were added and quickly passed through a sinter containing layers of Celite, silica and more Celite. The Et₂O was concentrated on the vacuum line without heating to yield (2*S*,4*S*)-2-ferrocenyl-3-pivaloyl-4-methyl-1,3-oxazolidin-5-one **5** as yellow crystals (3.42 g, 95%) with >98% de (>98% ee for the major diastereoisomer); *R*_f 0.38 (petroleum–Et₂O; 7:3); mp 104–105 °C; [α]_D²⁵ +24.3 (*c* 0.93, CHCl₃); ν_{max}(FT IR, KBr disc)/cm^{–1} 3099m, 2979m and 2962m (C–H), 1785s (OC=O), 1646s (NC=O), 1350s and 1194s; δ_H(200 MHz; CDCl₃) 1.27 [9H, s, C(CH₃)₃], 1.56 (3H, d, *J* 7, CHCH₃), 4.18–4.60 (4H, m, Cp), 4.25 (5H, s, Cp'), 4.64 (1H, q, *J* 7, CHCH₃) and 7.07 (1H, s, OCHN); δ_H(200 MHz; C₆D₆) 0.90 [9H, s, C(CH₃)₃], 1.26 (3H, d, *J* 7, CHCH₃), 3.86–3.91 (2H, m, Cp), 4.07 (5H, s, Cp'), 4.11–4.12 (1H, m, Cp), 4.23 (1H, q, *J* 7, CHCH₃), 4.70–4.71 (1H, m, Cp) and 7.10 (1H, s, OCHN); δ_C(50.3 MHz; CDCl₃) 20.05 (CHCH₃), 28.06 [C(CH₃)₃], 39.91 [C(CH₃)₃], 52.04 (CHCH₃),

65.23, 67.80, 68.43 and 69.29 (4 × CH in Cp), 69.19 (5 × CH in Cp'), 84.92 (quaternary C in Cp), 88.75 (OCHN), 173.55 and 175.84 (2 × C=O); *m/z* (EI) 369 [(M)⁺, 31%], 240 [(M – C₄H₉CO – CO₂)⁺, 39] and 57 [(C₄H₉)⁺, 100] (Found: C, 62.02; H, 6.02; N, 3.47. Calc. for C₁₉H₂₃NO₃Fe: C, 61.81; H, 6.28; N, 3.79%). Normally no ferrocenecarbaldehyde **3** was detected, however, it can easily be removed by washing with cold pentane.

General alkylation procedure to form (2*S*,4*R*)-2-ferrocenyl-3-pivaloyl-4-alkyl-4-methyl-1,3-oxazolidin-5-ones 7a–h

1.6 m BuⁿLi (1 equiv.) was added dropwise to a solution of diisopropylamine (1.1 equiv.) distilled from calcium hydride in THF at 0 °C and the mixture stirred for 15 min. The resulting solution was cooled to –78 °C and then transferred *via* cannula to a precooled (–78 °C) solution of the oxazolidinone **5** (1 equiv.) in THF. Then the appropriate alkyl bromide (1.3 equiv.) was added dropwise and the mixture stirred overnight up to room temperature. The reaction mixture was concentrated on the vacuum line. Several portions of Et₂O were added and quickly passed through a sinter containing layers of Celite, silica and more Celite. The Et₂O was concentrated on the vacuum line to yield (2*S*,4*R*)-2-ferrocenyl-3-pivaloyl-4-alkyl-4-methyl-1,3-oxazolidin-5-ones **7a–h** and the de of the crude reaction product was determined. Then the product was purified by washing with cold pentane.

(2*S*,4*R*)-2-Ferrocenyl-3-pivaloyl-4-benzyl-4-methyl-1,3-oxazolidin-5-one 7a. Starting with 3.0 g of the oxazolidinone **5** and following the general alkylation procedure using benzyl bromide as electrophile (2*S*,4*R*)-2-ferrocenyl-3-pivaloyl-4-benzyl-4-methyl-1,3-oxazolidin-5-one **7a** was obtained as yellow crystals (3.36 g, 90%) with >98% de (>98% ee for the major diastereomer); *R*_f 0.34 (petroleum–Et₂O, 8:2); mp 159–160 °C; [α]_D²⁵ –195.0 (*c* 1.0, CHCl₃); ν_{max}(FT IR, KBr disc)/cm^{–1} 3107m (C–H), 1790s (OC=O) and 1629s (NC=O); δ_H(300 MHz; CDCl₃) 0.81 [9H, s, C(CH₃)₃], 2.04 (3H, s, NCCH₃), 3.21 (1H, d, *J* 13.5, CH_AH_B), 3.81 (1H, d, *J* 13.5, CH_AH_B), 4.21–4.26 (4H, m, Cp), 4.28 (5H, s, Cp'), 6.10 (1H, s, OCHN) and 7.12–7.28 (5H, m, C₆H₅); δ_C(50.3 MHz; CDCl₃) 23.6 (NCCH₃), 28.1 [C(CH₃)₃], 40.8 [C(CH₃)₃], 41.3 (CH₂), 66.2, (NCMe), 67.9, 68.6, 68.7, 69.1 and 69.3 (9 × CH in Cp and Cp'), 86.7 (OCHN), 89.1 (quaternary C in Cp), 127.1, 128.3, 129.8, 136.1 (C₆H₅), 176.1 and 176.6 (2 × C=O); *m/z* 460 [(M + H)⁺, 100%], 459 [(M)⁺, 33], 331 (21), 330 [(M – C₄H₉CO – CO₂)⁺, 50] and 199 [(FeCH₂)⁺, 27] (Found: C, 67.79; H, 6.26; N, 3.28. Calc. for C₂₆H₂₉NO₃Fe: C, 67.98; H, 6.36; N, 3.05%).

(2*S*,4*R*)-2-Ferrocenyl-3-pivaloyl-4-allyl-4-methyl-1,3-oxazolidin-5-one 7b. Starting with 2.13 g of the oxazolidinone **5** and following the general alkylation procedure using distilled allyl bromide as electrophile (2*S*,4*R*)-2-ferrocenyl-3-pivaloyl-4-allyl-4-methyl-1,3-oxazolidin-5-one **7b** was obtained as orange crystals (1.84 g, 78%) with >96% de; *R*_f 0.82 (petroleum–Et₂O, 5:5); mp 167–169 °C; [α]_D²⁵ –218.2 (*c* 1.0, CHCl₃); ν_{max}(FT IR, KBr disc)/cm^{–1} 3090m (C–H), 1795s (OC=O), 1651s (NC=O), 1353s and 1186s; δ_H(300 MHz; CDCl₃) 1.05 [9H, s, C(CH₃)₃], 1.92 (3H, s, NCCH₃), 2.53 (1H, dd, *J* 4, 9.5, CH_AH_B), 3.36 (1H, dd, *J* 6, 9.5, CH_AH_B), 4.20–4.32 (4H, m, Cp), 4.23 (5H, s, Cp'), 5.10 (1H, s, CH=CH_AH_B), 5.15 (1H, d, *J* 2.5, CH=CH_AH_B), 5.47–5.61 (1H, m, CH₂CH=CH₂) and 6.66 (1H, s, OCHN); δ_C(50.3 MHz; CDCl₃) 22.87 (NCCH₃), 28.68 [C(CH₃)₃], 39.57 (CH₂), 41.09 [C(CH₃)₃], 64.71 (NCCH₃), 67.41, 68.08 and 69.05 (4 × CH in Cp), 69.20 (5 × CH in Cp'), 86.51 (OCHN), 89.77 (quaternary C in Cp), 120.04 (CH₂CH=CH₂), 131.62 (CH₂–CH=CH₂), 175.47 and 175.99 (2 × C=O); *m/z* (EI⁺) 410 [(M + H)⁺, 13%], 409 [(M)⁺, 73], 280 [(M – C₄H₉CO – CO₂)⁺, 37], 121 [(CpFe)⁺, 57] and 57 [(C₄H₉)⁺, 100] (Found: C, 64.53; H, 6.87; N, 3.36. Calc. for C₂₂H₂₇NO₃Fe: C, 64.56; H, 6.65; N, 3.42%).

(2*S*,4*R*)-2-Ferrocenyl-3-pivaloyl-4-[(*E*)-but-2-enyl]-4-methyl-1,3-oxazolidin-5-one 7c. Starting with 2.77 g of the oxazolidinone **5** and following the general alkylation procedure using

distilled crotyl bromide (*E*: *Z* ratio 9 : 1) as electrophile (2*S*,4*R*)-2-ferrocenyl-3-pivaloyl-4-(*but*-2-enyl)-4-methyl-1,3-oxazolidin-5-one **7c** was obtained as brown crystals (2.25 g, 71%) with 92% de and an *E*: *Z* ratio of 9 : 1; recrystallisation from Et₂O–hexane gave pure (2*S*,4*R*)-2-ferrocenyl-3-pivaloyl-4-(*E*)-*but*-2-enyl-4-methyl-1,3-oxazolidin-5-one **7c**; mp 114–118 °C; [α]_D²⁵ –91.0 (*c* 0.16, CHCl₃); ν_{\max} (FT IR, KBr disc)/cm⁻¹ 2975m (C–H), 1783s (OC=O), 1641s (NC=O), 1350m and 1182m; δ_{H} (500 MHz; CDCl₃) 1.04 [9H, s, C(CH₃)₃], 1.64 (3H, d, *J* 6.5, CH=CHCH₃), 1.89 (3H, s, NCCH₃), 2.45 (1H, dd, *J* 6, 14, CH_AH_B), 3.27 (1H, dd, *J* 9, 14, CH_AH_B), 4.20–4.31 (4H, m, Cp), 4.27 (5H, s, Cp'), 5.16 (1H, ddd, *J* 6, 9, 15, CH₂CH=CHCH₃), 5.52 (1H, dd, *J* 6.5, 15, CH₂CH=CHCH₃) and 6.64 (1H, s, OCHN); δ_{C} (125.7 MHz; CDCl₃) 18.00 and 22.85 (2 × CH₃), 28.68 [C(CH₃)₃], 38.51 (CH₂), 41.11 [C(CH₃)₃], 64.96 (NCCH₃), 67.39, 68.07, 69.04 and 69.07 (4 × CH in Cp), 69.21 (5 × CH in Cp'), 86.43 (OCHN), 89.96 (quaternary C in Cp), 124.25 and 130.59 (CH=CH), 175.71 and 175.86 (2 × C=O); *m/z* (APCI⁺) 424 [(M + H)⁺, 100%], 294 [(M – C₄H₉CO – CO₂)⁺, 49] and 199 [(FcCH₂)⁺, 24] [Found: C, 64.84; H, 6.87; N, 3.07. Calc. for C₂₃H₂₉NO₃Fe·0.2H₂O: C, 64.71; H, 6.94; N, 3.28%; HRMS: found: 424.158 646; required for (M + H)⁺: 424.157 508 (ppm –2.7)].

(2*S*,4*R*)-2-Ferrocenyl-3-pivaloyl-4-methyl-4-(2-methylbenzyl)-1,3-oxazolidin-5-one 7d. Starting with 2.09 g of the oxazolidinone **5** and following the general alkylation procedure using α -bromo-*o*-xylene as electrophile (2*S*,4*R*)-2-ferrocenyl-3-pivaloyl-4-methyl-4-(2-methylbenzyl)-1,3-oxazolidin-5-one **7d** was obtained as yellow crystals (2.38 g, 89%) with 96% de; mp 155–157 °C; [α]_D²³ –180.1 (*c* 1.10, CHCl₃); ν_{\max} (FT IR, KBr disc)/cm⁻¹ 2970m (C–H), 1790s (OC=O), 1627s (NC=O), 1336s and 1177s; δ_{H} (200 MHz; CDCl₃) 0.72 [9H, s, C(CH₃)₃], 2.08 (3H, s, NCCH₃), 2.36 (3H, s, C₆H₄CH₃), 3.28 (1H, d, *J* 14.5, CH_AH_B), 3.82 (1H, d, *J* 14.5, CH_AH_B), 4.21–4.32 (4H, m, Cp), 4.29 (5H, s, Cp'), 6.33 (1H, s, OCHN) and 7.02–7.13 (4H, m, C₆H₄CH₃); δ_{C} (50.3 MHz; CDCl₃) 19.63 and 24.28 (2 × CH₃), 27.86 [C(CH₃)₃], 37.55 (CH₂), 40.85 [C(CH₃)₃], 65.16 (NCCH₃), 67.78, 68.79 and 68.94 (4 × CH in Cp), 69.31 (5 × CH in Cp'), 86.93 (OCHN), 89.58 (quaternary C in Cp), 125.88, 126.93, 128.53 and 131.22 (4 × CH in C₆H₄), 134.93 and 138.18 (2 × quaternary C in C₆H₄), 176.64 and 176.71 (2 × C=O); *m/z* (CI, NH₃) 474 [(M + H)⁺, 100%] and 344 [(M – COC₄H₉ – CO₂)⁺, 26] [Found: C, 68.77; H, 6.80; N, 2.80. Calc. for C₂₇H₃₁NO₃Fe: C, 68.51; H, 6.60; N, 2.96%].

(2*S*,4*R*,*E*)-2-Ferrocenyl-3-pivaloyl-4-cinnamyl-4-methyl-1,3-oxazolidin-5-one 7e. Starting with 2.76 g of the oxazolidinone **5** and following the general alkylation procedure using cinnamyl bromide as electrophile (2*S*,4*R*,*E*)-2-ferrocenyl-3-pivaloyl-4-cinnamyl-4-methyl-1,3-oxazolidin-5-one **7e** was obtained as orange–brown crystals (3.41 g, 94%) with >98% de; mp 152–155 °C; [α]_D²³ –145.2 (*c* 0.27, CHCl₃); ν_{\max} (FT IR, KBr disc)/cm⁻¹ 2962m and 2930m (C–H), 1783s (OC=O), 1632s (NC=O), 1340s, 1242s and 1177s; δ_{H} (200 MHz; CDCl₃) 1.00 [9H, s, C(CH₃)₃], 1.97 (3H, s, NCCH₃), 2.70 (1H, ddd, *J* 1.5, 6, 14, CH_AH_B), 3.53 (1H, dd, *J* 9, 14, CH_AH_B), 4.21–4.31 (4H, m, Cp), 4.28 (5H, s, Cp'), 5.93 (1H, ddd, *J* 6, 9, 15, CH₂CH=CHPh), 6.45 (1H, d, *J* 15, CH₂CH=CHPh), 6.64 (1H, s, OCHN) and 7.21–7.35 (5H, m, C₆H₅); δ_{C} (50.3 MHz; CDCl₃) 22.83 (NCCH₃), 28.62 [C(CH₃)₃], 38.97 (CH₂), 41.10 [C(CH₃)₃], 65.05 (NCCH₃), 67.53, 67.71, 68.19 and 69.15 (4 × CH in Cp), 69.30 (5 × CH in Cp'), 86.67 (OCHN), 89.81 (quaternary C in Cp), 123.08, 126.38, 127.74, 128.79 and 135.15 (5 × CH in C₆H₅), 137.01 (quaternary C in C₆H₅), 175.99 and 176.43 (2 × C=O); *m/z* (CI, NH₃) 486 [(M + H)⁺, 18%], 215 [(FcCHO + H)⁺, 48], 199 [(FcCH₂)⁺, 51], 102 [(C₄H₉CO + NH₃)⁺, 100] and 85 [(C₄H₉CO)⁺, 53] [Found: C, 69.48; H, 6.67; N, 2.72. Calc. for C₂₈H₃₁NO₃Fe: C, 69.29; H, 6.44; N, 2.89%].

(2*S*,4*R*)-2-Ferrocenyl-3-pivaloyl-4-methyl-4-(2-naphthylmethyl)-1,3-oxazolidin-5-one 7f. Starting with 2.97 g of the oxazolidinone **5** and following the general alkylation procedure

using 2-(bromomethyl)naphthalene as a solution in THF, which was prepared by dissolving the electrophile in DCM, adding THF and removing the DCM *in vacuo*, (2*S*,4*R*)-2-ferrocenyl-3-pivaloyl-4-methyl-4-(2-naphthylmethyl)-1,3-oxazolidin-5-one **7f** was obtained as pale orange crystals (3.89 g, 95%) with >98% de; mp 155–158 °C; [α]_D²³ –49.6 (*c* 1.05, CHCl₃); ν_{\max} (FT IR, KBr disc)/cm⁻¹ 2979w (C–H), 1783s (OC=O), 1647m (NC=O), 1348m, 1248m and 1172m; δ_{H} (200 MHz; CDCl₃) 0.79 [9H, s, C(CH₃)₃], 2.10 (3H, s, NCCH₃), 3.36 (1H, d, *J* 13.5, CH_AH_B), 4.02 (1H, d, *J* 13.5, CH_AH_B), 4.22–4.30 (4H, m, Cp), 4.27 (5H, s, Cp'), 6.02 (1H, s, OCHN) and 7.26–7.85 (7H, m, C₁₀H₇); δ_{C} (50.3 MHz; CDCl₃) 23.63 (NCCH₃), 28.01 [C(CH₃)₃], 40.85 [C(CH₃)₃], 41.33 (CH₂), 66.50 (NCCH₃), 67.96, 68.67, 69.24 and 69.33 (9 × CH in Cp and Cp'), 86.82 (OCHN), 89.03 (quaternary C in Cp), 125.93, 126.31, 127.80, 127.90, 128.16 and 129.06 (7 × naphthalene CH), 132.75, 133.48 and 133.80 (3 × quaternary naphthalene C), 176.02 and 176.79 (2 × C=O); *m/z* (CI, NH₃) 510 [(M + H)⁺, 100%], 102 [(C₄H₉CO + NH₃)⁺, 63] and 85 [(C₄H₉CO)⁺, 61] [Found: C, 70.75; H, 6.49; N, 2.93. Calc. for C₃₀H₃₁NO₃Fe: C, 70.73; H, 6.13; N, 2.75%].

(2*S*,4*R*)-2-Ferrocenyl-3-pivaloyl-4-[1-(*tert*-butoxycarbonyl)-indol-3-ylmethyl]-4-methyl-1,3-oxazolidin-5-one 7g. Starting with 1.01 g of the oxazolidinone **5** and following the general alkylation procedure using 1-(*tert*-butoxycarbonyl)-3-(bromomethyl)indole¹³ as a solution in THF as electrophile (2*S*,4*R*)-2-ferrocenyl-3-pivaloyl-4-[1-(*tert*-butoxycarbonyl)indol-3-ylmethyl]-4-methyl-1,3-oxazolidin-5-one **7g** was obtained as beige crystals (1.34 g, 82%) with 96% de; mp 146–149 °C; [α]_D²³ –101.0 (*c* 0.43, CHCl₃); ν_{\max} (FT IR, KBr disc)/cm⁻¹ 2972m (C–H), 1789s (OC=O), 1726s (carbamate C=O), 1636s (NC=O), 1374s, 1178m and 1170m; δ_{H} (500 MHz; CDCl₃) 0.84 [9H, s, COC(CH₃)₃], 1.66 [9H, s, CO₂C(CH₃)₃], 2.10 (3H, s, NCCH₃), 3.31 (1H, d, *J* 14.5, CH_AH_B), 4.02 (1H, d, *J* 14.5, CH_AH_B), 4.20–4.29 (4H, m, Cp), 4.26 (5H, s, Cp'), 6.22 (1H, s, OCHN), 7.22–7.37 (3H, m, 3 × indole CH), 7.64 (1H, d, *J* 8, indole CH) and 8.15 (1H, d, *J* 8, indole CH); δ_{C} (125.7 MHz; CDCl₃) 23.44 (NCCH₃), 28.07 and 28.19 [2 × C(CH₃)₃], 31.72 (CH₂), 40.79 [COC(CH₃)₃], 65.35 (NCCH₃), 67.75, 68.68, 68.84 and 68.96 (4 × CH in Cp), 69.27 (5 × CH in Cp'), 83.60 [CO₂C(CH₃)₃], 86.74 (OCHN), 89.31 (quaternary C in Cp), 114.87, 120.16, 122.71, 124.44 and 125.47 (5 × indole CH), 130.20, 135.25 and 149.42 (3 × quaternary indole C), 176.08 and 176.20 (2 × C=O); *m/z* (CI, NH₃) 599 [(M + H)⁺, 27%], 130 [(C₉H₇N + H)⁺, 100] and 102 [(C₄H₉CO + NH₃)⁺, 47] [Found: C, 65.94; H, 6.35; N, 4.47. Calc. for C₃₃H₃₈N₂O₅Fe: C, 66.22; H, 6.40; N, 4.68%].

(2*S*,4*R*)-2-Ferrocenyl-3-pivaloyl-4-cyanomethyl-4-methyl-1,3-oxazolidin-5-one 7h. Starting with 1.64 g of the oxazolidinone **5** and following the general alkylation procedure using bromoacetonitrile as electrophile (2*S*,4*R*)-2-ferrocenyl-3-pivaloyl-4-cyanomethyl-4-methyl-1,3-oxazolidin-5-one **7h** was obtained as light brown crystals (1.56 g, 86%) with 92% de; mp 131–135 °C; [α]_D²¹ –230.0 (*c* 0.24, CHCl₃); ν_{\max} (FT IR, KBr disc)/cm⁻¹ 2990m and 2940m (C–H), 2248w (C≡N), 1792s (OC=O), 1639s (NC=O), 1397m, 1343s and 1193s; δ_{H} (200 MHz; CDCl₃) 1.13 [9H, s, C(CH₃)₃], 1.95 (3H, s, NCCH₃), 2.90 (1H, d, *J* 16.5, CH_AH_B), 3.84 (1H, d, *J* 16.5, CH_AH_B), 4.20–4.38 (4H, m, Cp), 4.28 (5H, s, Cp') and 6.89 (1H, s, OCHN); δ_{C} (125.7 MHz; CDCl₃) 22.30 (NCCH₃), 25.66 (CH₂), 28.48 [C(CH₃)₃], 41.39 [C(CH₃)₃], 62.12 (NCCH₃), 67.69, 68.19, 68.82 and 69.51 (4 × CH in Cp), 69.31 (5 × CH in Cp'), 87.55 (OCHN) and 88.74 (quaternary C in Cp), 115.56 (C≡N), 173.17 and 177.20 (2 × C=O); *m/z* (EI) 408 [(M)⁺, 20%], 279 [(M – C₄H₉CO – CO₂)⁺, 36], 121 [(C₅H₅Fe)⁺, 42] and 57 [(C₄H₉)⁺, 100] [Found: C, 61.99; H, 5.62; N, 6.69. Calc. for C₂₁H₂₄N₂O₃Fe: C, 61.78; H, 5.92; N, 6.86%].

General hydrolysis procedure to form the free α -methyl- α -amino acids 8a–h

A glass column was filled with distilled water, Amberlyst-15

(wet) was added slowly and in several portions into the column. It was washed with distilled water up to pH ~ 2–4 and then with acetone–distilled water (9:1). Compounds **7a–h** were dissolved in acetone–distilled water (9:1); a gentle warming was sometimes needed to complete dissolution. The resulting solution was poured into the column and left for 12 h. Elution of the Amberlyst column with acetone–distilled water (9:1), concentration of the acetone *in vacuo*, followed by extraction of the aqueous solution with Et₂O and purification by flash column chromatography (SiO₂; petroleum–Et₂O, 9:1) yielded ferrocenecarbaldehyde **3**. The Amberlyst column was then eluted with 2 M NH₄OH. The aqueous solution was concentrated *in vacuo* to yield the free α -methyl- α -amino acid **8a–h**.

(R)- α -Methylphenylalanine 8a.^{1b,3b,4b,6b,14} Starting with 3.0 g of (2*S*,4*R*)-2-ferrocenyl-3-pivaloyl-4-benzyl-4-methyl-1,3-oxazolidin-5-one **7a** and following the general hydrolysis procedure, ferrocenecarbaldehyde **3** (1.33 g, 95%) and the free amino acid **8a** were obtained. The free amino acid **8a** was dissolved in MeOH and passed through a sinter containing decolorising charcoal to yield after removal of the solvent (R)- α -methylphenylalanine **8a** as colourless crystals (0.89 g, 76%); [α]_D²⁵ +17.0 (c 0.1, MeOH) {lit.,^{4b} [α]_D²⁴ +20.0 (c 0.1, MeOH), lit.,^{6b} [α]_D²⁵ +19.0 (c 0.1, MeOH)}. (R)- α -Methylphenylalanine **8a** proved difficult to dehydrate, showed a tendency to rehydrate and was easily oxidisable by air. Therefore the hydrochloride salt of **8a** was prepared as described in ref. 3b; ν_{\max} (FT IR, KBr disc)/cm⁻¹ 3436m (N–H), 3034m br (OCO–H and C–H), 1619s (C=O) and 1583m (C=C); δ_{H} (200 MHz; MeOD) 1.50 (3H, s, CH₃), 2.92 (1H, d, *J* 14, CH_AH_B), 3.28 (1H, d, *J* 14, CH_AH_B) and 7.29 (5H, m, C₆H₅); δ_{C} (50.3 MHz; MeOD) 21.5 (CH₃), 42.6 (CH₂), 60.7 (CCH₃), 127.6, 128.7, 130.2 and 134.1 (5 \times CH in C₆H₅) and 173.9 (C=O); *m/z* 180 [(M + H)⁺, 100%], 134 [(M – CO₂H)⁺, 16] and 88 [(M – C₃H₇)⁺, 21] (Found: C, 55.86; H, 6.77; N, 6.72. Calc. for C₁₀H₁₄NO₂Cl: C, 55.69; H, 6.54; N, 6.49%).

(R)- α -Allyl- α -alanine 8b.^{14b,15} Starting with 1.84 g of (2*S*,4*R*)-2-ferrocenyl-3-pivaloyl-4-allyl-4-methyl-1,3-oxazolidin-5-one **7b** and following the general hydrolysis procedure, ferrocenecarbaldehyde **3** (0.82 g, 85%) and the free amino acid **8b** were obtained. The free amino acid **8b** was purified by ion-exchange column chromatography using Dowex (50WX8-200) to yield (R)- α -allyl- α -alanine **8b** as white crystals (0.55 g, 95%); mp 296–299 °C (lit.,^{15a} mp 300 °C, lit.,^{14b} mp 308 °C); [α]_D²⁵ +24.1 (c 0.7, MeOH) {lit.,^{15b} (S)-enantiomer: [α]_D²⁰ –25.7 (c 0.8, MeOH)}; ν_{\max} (FT IR, KBr disc)/cm⁻¹ 3509m br (N–H), 3021s br (OCO–H and C–H), 1645s (C=O), 1575s and 1545s; δ_{H} (200 MHz; D₂O) 1.47 (3H, s, CH₃), 2.43 (1H, dd, *J* 8, 14.5, CH_AH_B), 2.65 (1H, dd, *J* 6.5, 14.5, CH_AH_B), 5.22 (1H, d, *J* 4, CH=CH_AH_B), 5.28 (1H, s, CH=CH_AH_B) and 5.63–5.84 (1H, m, CH=CH₂); δ_{C} (50.3 MHz; MeOD) 21.40 (CH₃), 41.49 (CH₂CH=CH₂), 59.96 (CCH₃), 120.05 (CH₂CH=CH₂) and 131.20 (CH₂CH=CH₂); *m/z* (DCI, NH₃) 130 [(M + H)⁺, 100%], 88 [(M – C₃H₇)⁺, 21] and 84 [(M – CO₂H)⁺, 17] [HRMS: Found 130.086 589; required for (M + H)⁺, 130.086 804 (ppm 1.7)].

(R)- α -[(*E*)-But-2-enyl]- α -alanine 8c. Starting with 1.41 g of (2*S*,4*R*)-2-ferrocenyl-3-pivaloyl-4-[(*E*)-but-2-enyl]-4-methyl-1,3-oxazolidin-5-one **7c** and following the general hydrolysis procedure, ferrocenecarbaldehyde **3** (0.59 g, 83%) and the free amino acid **8c** were obtained. The free amino acid **8c** was purified by ion-exchange column chromatography using Dowex (50WX8-200) to yield (R)- α -[(*E*)-but-2-enyl]- α -alanine **8c** as beige crystals (0.37 g, 78%); mp 255–258 °C; [α]_D²¹ +11.5 (c 0.2, MeOH); ν_{\max} (FT IR, KBr disc)/cm⁻¹ 3423m br (N–H), 2921m br (OCO–H and C–H), 1618s (C=O) and 1400s; δ_{H} (500 MHz; CD₃OD) 1.43 (3H, s, CH₃), 1.69 (3H, d, *J* 6.5, CH=CHCH₃), 2.33 (1H, dd, *J* 8, 14.5, CH_AH_B), 2.58 (1H, ddd, *J* 1, 6.5, 14.5, CH_AH_B), 5.43 (1H, ddd, *J* 6.5, 8, 15, CH₂CH=CHCH₃) and 5.66 (1H, dd, *J* 6.5, 15, CH₂CH=CHCH₃); δ_{C} (125.7 MHz; MeOD) 18.25 and 23.03 (2 \times CH₃), 41.97 (CH₂), 61.99 (CCH₃),

125.05 and 132.41 (CH=CH) and 176.41 (C=O); *m/z* (electrospray⁺) 144 [(M + H)⁺, 100%] [HRMS: Found 144.102 873; required for (M + H)⁺, 144.102 454 (ppm –2.9)].

(R)- α ,2-Dimethylphenylalanine 8d. Starting with 0.71 g of (2*S*,4*R*)-2-ferrocenyl-3-pivaloyl-4-methyl-4-(2-methylbenzyl)-1,3-oxazolidin-5-one **7d** and following the general hydrolysis procedure, ferrocenecarbaldehyde **3** (0.29 g, 90%) and the free amino acid **8d** were obtained. The free amino acid **8d** was purified by ion-exchange column chromatography using Dowex (50WX8-200) to yield (R)- α ,2-dimethylphenylalanine **8d** as white crystals (0.22 g, 76%); mp 226–228 °C; [α]_D²² +11.5 (c 0.9, MeOH); ν_{\max} (FT IR, KBr disc)/cm⁻¹ 3419m br (N–H), 3138m br, 2943m br and 2757m br (OCO–H and C–H), 1618s (C=O), 1590s, 1549s and 1518s (aromatic C=C), 1378s and 748m (aromatic C–H); δ_{H} (200 MHz; CD₃OD) 1.47 (3H, s, CH₃), 2.36 (1H, s, C₆H₄CH₃), 3.16 (2H, br s, CH₂) and 7.11–7.27 (4H, m, C₆H₄); δ_{H} (200 MHz; D₂O) 1.30 and 2.09 (6H, 2 \times s, 2 \times CH₃), 2.91 (1H, d, *J* 14.5, CH_AH_B), 3.02 (1H, d, *J* 14.5, CH_AH_B) and 6.96–7.04 (4H, m, C₆H₄); δ_{C} (125.7 MHz; MeOD) 20.25 and 23.17 (2 \times CH₃), 40.52 (CH₂), 63.09 (CCH₃), 127.15, 128.44 and 131.91 (4 \times aromatic CH) and 176.29 (C=O); *m/z* (CI, NH₃) 194 [(M + H)⁺, 79%], 148 [(M – CO₂H)⁺, 47] and 88 [(M – CH₂-C₆H₄CH₃)⁺, 100] [HRMS: found 194.118 715; required for (M + H)⁺, 194.118 104 (ppm –3.1)].

(2*R*,4*E*)-2-Amino-2-methyl-5-phenylpent-4-enoic acid 8e.¹⁶ Starting with 1.96 g of (2*S*,4*R*,*E*)-2-ferrocenyl-3-pivaloyl-4-cinnamyl-4-methyl-1,3-oxazolidin-5-one **7e** and following the general hydrolysis procedure, ferrocenecarbaldehyde **3** (0.71 g, 82%) and the free amino acid **8e** were obtained. The free amino acid **8e** was purified by ion-exchange column chromatography using Dowex (50WX8-200) to yield (2*R*,4*E*)-2-amino-2-methyl-5-phenylpent-4-enoic acid **8e** as beige crystals (0.59 g, 71%); mp 241–245 °C; [α]_D²¹ +13.1 (c 0.4, MeOH); ν_{\max} (FT IR, KBr disc)/cm⁻¹ 3431m br (N–H), 3026m br (OCO–H and C–H), 1612s (C=O) and 1400s; δ_{H} (400 MHz; CD₃OD) 1.49 (3H, s, CH₃), 2.57 (1H, ddd, *J* 0.5, 8.5, 14.5, CH_AH_B), 2.80 (1H, ddd, *J* 1.0, 7.0, 14.5, CH_AH_B), 6.22 (1H, ddd, *J* 7.0, 8.5, 15.5, CH₂CH=CHPh), 6.56 (1H, br d, *J* 15.5, CH₂CH=CHPh) and 7.17–7.83 (5H, m, C₆H₅); δ_{C} (100.6 MHz; MeOD) 23.25 (CH₃), 42.43 (CH₂), 62.14 (CCH₃), 123.82, 127.48, 128.31, 129.50 and 136.36 (CH=CH and 5 \times CH in C₆H₅), 138.37 (quaternary C in C₆H₅) and 176.29 (C=O); *m/z* (CI⁺) 206 [(M + H)⁺, 100%], 160 [(M – CO₂H)⁺, 7] and 88 [(M – CH₂CH=CHC₆H₅)⁺, 9] [HRMS: Found 206.118 760; required for (M + H)⁺, 206.118 104 (ppm –3.2)].

(R)- α -(2-Naphthylmethyl)alanine 8f.¹⁷ (2*S*,4*R*)-2-Ferrocenyl-3-pivaloyl-4-methyl-4-(2-naphthylmethyl)-1,3-oxazolidin-5-one **7f** (1.37 g, 2.69 mmol) was dissolved in acetone–distilled water (9:1) (100 ml). To this solution Amberlyst-15 (wet) (120 ml), previously washed with distilled water up to pH ~ 2–4 and then twice with acetone–distilled water (9:1), was added. The reaction mixture was placed under argon and to ensure the complete exclusion of oxygen argon was bubbled through the reaction mixture for 10 min. After leaving the reaction mixture for 12 h under a positive pressure of argon it was poured into a glass column. Elution of the Amberlyst with acetone–distilled water (9:1), concentration of the acetone *in vacuo*, followed by extraction of the aqueous solution with Et₂O and purification by flash column chromatography (SiO₂; petroleum–Et₂O, 9:1) yielded ferrocenecarbaldehyde **3** (0.47 g, 82%). The Amberlyst was then eluted with 2 M NH₄OH. The aqueous solution was concentrated *in vacuo* to yield the free amino acid **8f** which was purified by Dowex (50WX8-200) ion-exchange column chromatography to obtain (R)- α -(2-naphthylmethyl)alanine **8f** as white crystals (0.49 g, 79%); mp 238–241 °C (lit.,^{17a} mp 259 °C); [α]_D²² +18.1 (c 0.16, MeOH), [α]_D²² +14.9 (c 0.73, 1 M HCl) {lit.,^{17a} [α]_D²⁰ +11.8 (c 1.0, 1 M HCl), lit.,^{17b} [α]_D +14.3 (1 M HCl)}; ν_{\max} (FT IR, KBr disc)/cm⁻¹ 3436m br and 3268m br (N–H), 3052m br (OCO–H and C–H), 1577s (C=O), 1534m and 1507m (aromatic C=C) and 1404m; δ_{H} (200 MHz; MeOD) 1.56 (3H, s, CH₃), 3.10

(1H, d, J 14, CH_AH_B), 3.45 (1H, d, J 14, CH_AH_B) and 7.41–7.84 (7H, m, $C_{10}H_7$); δ_C (125.7 MHz; MeOD) 23.64 (CH_3), 44.46 (CH_2), 63.01 (CCH_3), 126.95, 127.17, 128.62, 128.83, 129.27, 129.31 and 130.25 ($7 \times$ naphthalene CH), 133.66, 134.26 and 134.99 ($3 \times$ quaternary naphthalene C) and 176.02 (C=O); m/z (APCI⁺) 230 [(M + H)⁺, 100%], 213 [(M - NH₂)⁺, 13] and 184 [(M - CO₂H)⁺, 85] [HRMS: Found 230.118 012; required for (M + H)⁺, 230.118 104 (ppm 0.4)].

This hydrolysis reaction had to be performed under an inert atmosphere of oxygen free argon, otherwise the byproduct 2-pivaloylamino-2-methyl-3-(naphthalen-2-yl)propionic acid was obtained as a brown solid; mp 159–164 °C; [α]_D²³ -68.4 (c 0.16, MeOH); ν_{max} (FT IR, KBr disc)/cm⁻¹ 3407m br (OCN-H), 2963m br (OCO-H and C-H), 1654s br (OC=O and NC=O first band), 1509s (NC=O second band) and 1407m; δ_H (500 MHz; MeOD) 1.04 [9H, s, C(CH₃)₃], 1.67 (3H, s, CH₃), 3.39 (1H, d, J 13, CH_AH_B), 3.67 (1H, d, J 13, CH_AH_B), 4.57 (1H, br s, NH) and 7.31–7.76 (7H, m, $C_{10}H_7$); δ_C (50.3 MHz; CDCl₃) 23.38 (CH_3), 27.30 [C(CH₃)₃], 39.15 [C(CH₃)₃], 40.73 (CH_2), 61.12 (CCH_3), 125.75, 126.13, 127.77, 128.34 and 129.07 ($7 \times$ naphthalene CH), 132.63, 133.48 and 134.24 ($3 \times$ quaternary naphthalene C), 177.68 and 179.37 ($2 \times$ C=O); m/z (APCI⁺) 314 [(M + H)⁺, 100%], 268 [(M - CO₂H)⁺, 40] and 184 [(M - COC₄H₉ - CO₂)⁺, 34] [HRMS: Found 314.175 792; required for (M + H)⁺, 314.175 619 (ppm -0.6)]. This amide byproduct could be converted into the free amino acid **8f** in 60% yield by stirring with two equivalents of Meerwein's salt in DCM at room temp. overnight followed by extraction of the product into distilled water.

(R)- α -Methyltryptophan **8g**,^{18,4b} (2*S*,4*R*)-2-Ferrocenyl-3-pivaloyl-4-[1-(*tert*-butoxycarbonyl)indol-3-ylmethyl]-4-methyl-1,3-oxazolidin-5-one **7g** (0.87 g, 1.45 mmol) was dissolved in acetone–distilled water (9:1) (60 ml). To this solution Amberlyst-15 (wet) (80 ml), previously washed with distilled water up to pH ~2–4 and then twice with acetone–distilled water (9:1), was added. The reaction mixture was placed under argon and to ensure the complete exclusion of oxygen argon was bubbled through the reaction mixture for 10 min. After leaving the reaction mixture for 12 h under a positive pressure of argon it was poured into a glass column. Elution of the Amberlyst with acetone–distilled water (9:1), concentration of the acetone *in vacuo*, followed by extraction of the aqueous solution with Et₂O and purification by flash column chromatography (SiO₂; petroleum–Et₂O, 9:1) yielded ferrocenecarbaldehyde **3** (0.25 g, 80%). The Amberlyst was then eluted with 2 M NH₄OH. The aqueous solution was concentrated *in vacuo* to yield a mixture of alanine and the free amino acid **8g** which was purified by slow Dowex (50WX8-200) ion-exchange column chromatography to obtain (R)- α -methyltryptophan **8g** as white crystals (0.16 g, 50%); mp 238–242 °C (decomp.) (lit.,^{18a} mp 235–237 °C); [α]_D²² +14.1 (c 0.33, MeOH), [α]_D²² +16.5 (c 0.09, H₂O) {lit.,^{18a} [α]_D²² +16 (c 1, MeOH), lit.,^{4b} (*S*)-enantiomer: [α]_D²² -10.6 (c 0.9, H₂O)}; ν_{max} (FT IR, KBr disc)/cm⁻¹ 3416s br (N-H), 3152s br and 3049s br (OCO-H and C-H), 1622s (C=O) and 1404s; δ_H (500 MHz; MeOD) 1.54 (3H, s, CH₃), 3.20 (1H, d, J 15, CH_AH_B), 3.38 (1H, d, J 15, CH_AH_B), 7.04 (1H, dt, J 1, 8, indole CH), 7.10 (1H, dt, J 1, 8, indole CH), 7.21 (1H, s, indole CH), 7.35 (1H, d, J 8, indole CH) and 7.67 (1H, d, J 8, indole CH); δ_C (125.7 MHz; MeOD) 23.30 (CH_3), 34.02 (CH_2), 63.20 (CCH_3), 108.58, 129.44 and 137.97 ($3 \times$ quaternary indole C), 112.32, 119.64, 120.12, 122.53 and 125.88 ($5 \times$ indole CH) and 176.92 (C=O); m/z (APCI⁺) 219 [(M + H)⁺, 64%], 202 [(M - NH₂)⁺, 93], 173 [(M - CO₂H)⁺, 53] and 130 [(C₉H₈N)⁺, 100] [HRMS: Found 219.114 012; required for (M + H)⁺, 219.113 353 (ppm -3.0)].

This hydrolysis reaction had to be performed under an inert atmosphere of oxygen free argon, otherwise the byproduct 2-pivaloylamino-3-(indol-3-yl)-2-methylpropionic acid was obtained as a brown solid; mp 175–181 °C; [α]_D²² -40.4 (c 0.24, MeOH); ν_{max} (FT IR, KBr disc)/cm⁻¹ 3413m br (OCN-H and

N-H), 2977m br (OCO-H and C-H), 1734s (OC=O), 1642s (NC=O first band), 1513m (NC=O second band), 1454s and 1368s; δ_H (500 MHz; C₆D₅CD₃; 90 °C) 1.43 [9H, s, C(CH₃)₃], 1.74 (3H, s, CH₃), 3.58 (1H, d, J 14, CH_AH_B), 3.88 (1H, d, J 14, CH_AH_B), 6.47 (1H, br s, NH), 7.09 (1H, t, J 7, indole CH), 7.14 (1H, t, J 7, indole CH), 7.58 (1H, s, indole CH), 7.72 (1H, d, J 7, indole CH) and 8.21 (1H, d, J 7, indole CH); m/z (APCI⁺) 303 [(M + H)⁺, 52%], 257 [(M - CO₂H)⁺, 20] and 130 [(C₉H₈N)⁺, 100] [HRMS: found 303.172 034; required for (M + H)⁺, 303.170 868 (ppm -3.8)].

(R)-2-Amino-3-cyano-2-methylpropionic acid **8h**. Starting with 0.69 g of (2*S*,4*R*)-2-ferrocenyl-3-pivaloyl-4-cyanomethyl-4-methyl-1,3-oxazolidin-5-one **7h** and following the general hydrolysis procedure, ferrocenecarbaldehyde **3** (0.29 g, 80%) and the free amino acid **8h** were obtained. The free amino acid **8h** was purified by ion-exchange column chromatography using Dowex (50WX8-200) to yield (R)-2-amino-3-cyano-2-methylpropionic acid **8h** as white crystals (0.18 g, 83%); mp 114–121 and 208–215 °C; [α]_D²³ -20.0 (c 1.1, MeOH); ν_{max} (FT IR, KBr disc)/cm⁻¹ 3436s br (N-H), 3153s br (OCO-H and C-H), 1682s (C=O) and 1401s; δ_H (200 MHz; D₂O) 1.24 (3H, s, CH₃), 2.46 (1H, d, J 16.5, CH_AH_B) and 2.69 (1H, d, J 16.5, CH_AH_B); δ_C (125.7 MHz; D₂O) 22.65 (CH_3), 40.00 (CH_2), 59.32 (CCH_3), 174.94 and 176.24 (C=O and C=N); m/z (electrospray⁻) 145 [(M - H + H₂O)⁺, 100%], 127 [(M - H)⁺, 52] and 113 [33] [HRMS: Found 129.066 895; required for (M + H)⁺, 129.066 403 (ppm -3.8)].

Crystal data for (2*RS*,4*RS*)-5

C₁₉H₂₃Fe₁N₁O₃, $M = 369.2$, monoclinic, $a = 12.1263(9)$, $b = 10.9063(6)$, $c = 13.946(1)$ Å, $\beta = 108.374(6)^\circ$, $U = 1750$ Å³ (by least squares refinement on the diffractometer angles for 25 automatically centred reflections, $\lambda = 0.71069$ Å), space group $P2_1/a$, $Z = 4$, $F(000) = 776$, $D_x = 1.40$ g cm⁻³. Yellow rectangular prisms. Crystal dimensions: 0.31 × 0.56 × 0.68 mm, $\mu(\text{Mo-K}\alpha) = 8.72$ cm⁻¹.

Data were measured on an Enraf-Nonius CAD4 diffractometer using graphite monochromated Mo-K α radiation and an ω - 2θ scan (ω scan width = 0.75 + 0.35 tan θ , ω scan speed 1.3–6.7 deg min⁻¹). † Data were corrected for Lorentz and polarisation effects and an empirical absorption correction based on azimuthal scan data applied (min, max transmission factors = 1.16, 1.27). A total of 4827 reflections ($1 \leq \theta \leq 27^\circ$, $-15 \leq h \leq 15$, $-1 \leq k \leq 13$, $-1 \leq l \leq 17$) were measured, of which 3814 were unique (merging $R = 0.024$) and 3077 were observed with $I \geq 3\sigma(I)$. Three standard reflections measured every hour showed no appreciable decay.

The non-hydrogen atoms were located by Patterson¹⁹ and difference Fourier syntheses. The structure was refined using full matrix least squares with anisotropic thermal parameters for all non-hydrogen atoms. The hydrogen atoms were placed in calculated positions (C-H = 1.00 Å and $U_{iso} = 1.25 U_{eq}$ of adjacent atom) and were not included in the final cycles of refinement. A four term Chebyshev weighting scheme²⁰ was applied which gave satisfactory agreement analyses. At convergence, $R = 0.034$ and $R_w = 0.039$ for 217 parameters.

All calculations were performed using the Oxford CRYSTALS²¹ program package on a 486 personal computer.

Crystal data for (2*RS*,4*SR*)-7a

C₂₆H₂₉Fe₁N₁O₃, $M = 459.4$, monoclinic, $a = 18.305(1)$, $b = 6.3831(4)$, $c = 21.109(1)$ Å, $\beta = 112.005(6)^\circ$, $U = 2287$ Å³ (by

† Full crystallographic details, excluding structure factor tables, for compounds (2*RS*,4*RS*)-5 and (2*RS*,4*SR*)-7a have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, available via the RSC Web pages (<http://www.rsc.org/authors>). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/167.

least squares refinement on the diffractometer angles for 25 automatically centred reflections, $\lambda = 0.710\ 69\ \text{\AA}$), Space group $P2_1/a$, $Z = 4$, $F(000) = 968$, $D_x = 1.34\ \text{g cm}^{-3}$. Orange rectangular prisms. Crystal dimensions: $0.37 \times 0.74 \times 0.19\ \text{mm}$, $\mu(\text{Mo-K}\alpha) = 6.83\ \text{cm}^{-1}$.

Data were measured and processed as before. A total of 5769 reflections were measured ($1 \leq \theta \leq 26^\circ$, $-22 \leq h \leq 22$, $-1 \leq k \leq 7$, $-1 \leq l \leq 26$), of which 4477 were unique (merging $R = 0.017$) and 3006 were observed with $I \geq 3\sigma(I)$.

The structure was solved as before and refined with anisotropic thermal parameters for all non-hydrogen atoms. The carbon atoms of the phenyl ring and unsubstituted Cp ring were subject to 'soft' restraints²² during refinement. A three term Chebyshev weighting scheme²⁰ was applied which gave satisfactory agreement analyses. At convergence $R = 0.039$ and $R_w = 0.044$ for 280 parameters.

All calculations were performed using the Oxford CRYSTALS²¹ program package on a MicroVAX 3800 computer. Atomic scattering factors were taken from the usual sources.²³

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