Kinetic and thermodynamic control in the stereoselective formation of *trans*- and *cis*-2-ferrocenyl-3-pivaloyl-4-alkyl-1,3-oxazolidin-5-ones

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Received 19th August 2008, Accepted 22nd September 2008
First published as an Advance Article on the web 4th December 2008
DOI: 10.1039/b814450h

A range of ferrocenylimines derived from ferrocenecarboxaldehyde and the α-amino acids (*S*)-alanine, (*S*)-2-aminobutyric acid, (*S*)-norvaline, (*R*)-2-phenylglycine, (*S*)-phenylalanine, *O*-benzyl (*S*)-serine, and (*S*)-tryptophan can be cyclised stereoselectively to afford either the corresponding *cis*- or *trans*-2-ferrocenyl-3-pivaloyl-4-alkyl-1,3-oxazolidin-5-ones. The cyclisation reaction shows marked temperature dependence, giving rise preferentially to the *trans*-oxazolidinone under kinetic control (−78 °C) and the thermodynamic *cis*-oxazolidinone at −15 °C to rt.

Introduction

α,α-Disubstituted α-amino acids are potent inhibitors of enzymes that metabolise the corresponding proteinogenic amino acids.[1] As a consequence, a plethora of methods have emerged in recent years for the asymmetric synthesis of this molecular class, with the employment of chiral auxiliaries being perhaps the most utilised strategy within this field.[2] Among the many protocols that have been developed for this purpose, the use of Seebach's elegant concept of self-regeneration of stereocentres (SRS)[3] is perhaps the most widely applied.[4] For example, condensation of the sodium salt of alanine with pivalaldehyde affords imine **1**, which upon treatment with benzoyl chloride generates an 83 : 17 mixture of the corresponding *cis*- and *trans*-oxazolidinones, with the *cis*-oxazolidinone predominating. Separation of these diastereoisomers and subsequent deprotonation of the *cis*-oxazolidinone **2** with a lithium amide base, and stereoselective alkylation of the resultant enolate **3** gives the corresponding disubstituted oxazolidinone **4** with high stereocontrol. Subsequent hydrolysis yields the corresponding constituent amino acid **5** (Fig. 1).

Analysis of the literature concerning the stereoselectivity of oxazolidinone formation using the SRS strategy indicates that the *cis*- and *trans*-oxazolidinone ratio is highly dependent upon a number of factors including the C(2)-substituent of the α-amino acid, the aldehyde used to promote the cyclisation, the acylating agent and the reaction conditions.[5] For example, using alanine as the starting material, a range of *cis* : *trans*-oxazolidinone ratios have been noted with variation in the aldehyde and acyl fragment. Using *N*-benzoyl promotion of the cyclisation, an 83 : 17 *cis*:*trans*-ratio is observed using pivalaldehyde, while with benzaldehyde the *trans*-oxazolidinone predominates (*cis* : *trans* 12 : 88). Furthermore, using *N*-benzoyl protection and pivalaldehyde and varying the alkyl stereodirecting group of the amino acid, the corresponding *cis*-oxazolidinones predominate with stereoselectivities ranging from 71 : 29 to 83 : 17,[6] while using benzaldehyde, the

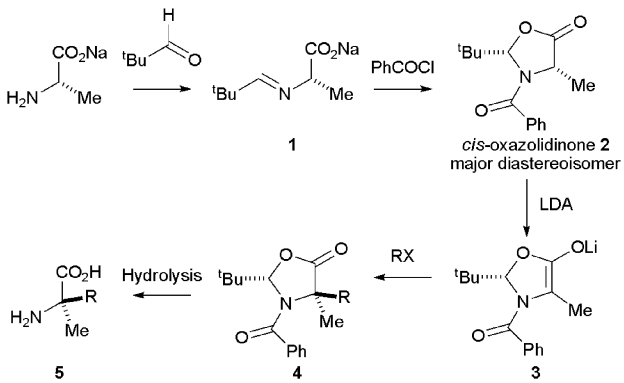

Fig. 1 SRS strategy for the preparation of α,α-disubstituted α-amino acids.

trans-diastereoisomer is generally favoured with stereoselectivities ranging from 25 : 75 to 12 : 88 (Fig. 2).[7]

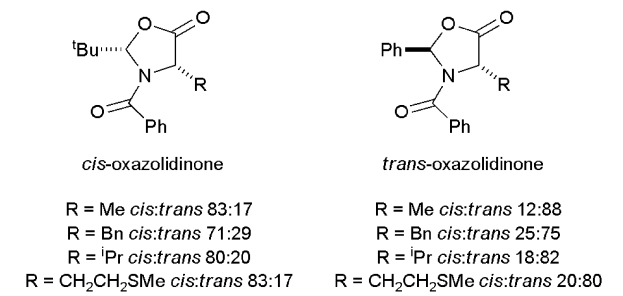

Fig. 2 *cis*- and *trans*-oxazolidinone formation.

Only limited analytical studies have been conducted that investigate the origin of this *cis* : *trans*-preference in oxazolidinone formation. Although α-amino *N*-methylamides may be cyclised to give either the *cis*- or *trans*-imidazolidinones preferentially,[8] the corresponding analysis has not been considered using oxazolidinones. However, Napolitano and Farina have recently shown that a variety of acidic conditions can be used to yield an equilibrium mixture of the *cis*- and *trans*-oxazolidinones derived from alanine, with the highest selectivity for the *cis*-isomer observed using $ZnCl_2$ and an *N*-methoxycarbonyl protecting group (Fig. 3).[9]

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R	X	*cis* : *trans*
Ph	Ph	60:40
Ph	OMe	85:15
4'-biphenyl	OMe	85:15

Fig. 3 Equilibrium investigations of *cis* : *trans* oxazolidinones.

Previous investigations from this laboratory[10] have shown that *cis*-(2*S*,4*S*)-2-ferrocenyl-3-pivaloyl-4-methyl-1,3-oxazolidin-5-one **7**, prepared as a single diastereoisomer upon treatment of imine **6** [derived from (*S*)-alanine and ferrocenecarboxaldehyde] with pivaloyl chloride, may be used for the asymmetric synthesis of α-alkyl-α-methyl-α-amino acids.[10a,b] Deprotonation of **7**, followed by alkylation of enolate **8** leads to the corresponding oxazolidinones **9** with exceptionally high stereoselectivity, with mild acid hydrolysis using Amberlyst resin promoted by neighbouring group participation of the ferrocenyl group giving the desired α-alkyl-α-methyl-α-amino acids **10** in high ee (Fig. 4).

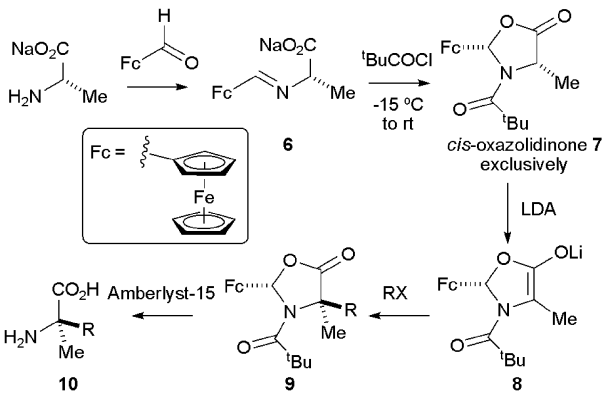


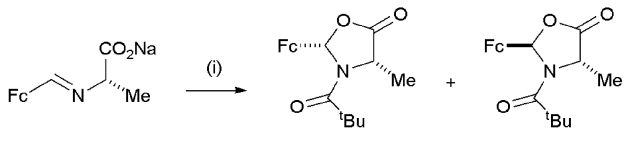
Fig. 4 Synthetic application of (2*S*,4*S*)-2-ferrocenyl-3-pivaloyl-4-methyl-1,3-oxazolidin-5-one **7**.

In this manuscript, we wish to delineate our observations concerning the stereoselective synthesis and thermodynamic stability of a series of *cis*- and *trans*-2-ferrocenyl-3-pivaloyl-4-alkyl-1,3-oxazolidin-5-ones. By judicious choice of the reaction temperature, the *trans*-isomer is available under kinetic control while the *cis*-isomer can be obtained from thermodynamic control.

Results and discussion

Model studies: probing kinetic and thermodynamic control in oxazolidinone formation from (*S*)-alanine

Stereoselective oxazolidinone formation was initially studied using the imine **6** as a model system for reaction analysis. Addition of pivaloyl chloride to imine **6** at –15 °C and warming the reaction mixture to rt overnight gave a crude product containing *cis*-(2*S*,4*S*)-2-ferrocenyl-3-pivaloyl-4-methyl-1,3-oxazolidin-5-one **7** virtually exclusively (>98% de), with crystallisation from pentane giving *cis*-(2*S*,4*S*)-**7** in 95% isolated yield as a single diastereoisomer. However, addition of pivaloyl chloride to imine **6** at –20 °C and subsequent maintenance of the reaction at this temperature overnight gave a 40 : 60 mixture of *cis*-(2*S*,4*S*)-**7** and *trans*-(2*R*,4*S*)-**11**. Carrying out this reaction at –78 °C gave a 12 : 88 mixture of *cis*-(2*S*,4*S*)-**7** and *trans*-(2*R*,4*S*)-**11**, with *trans*-(2*R*,4*S*)-**11** isolated in 85% yield as a single diastereoisomer after crystallisation (Scheme 1).



Reaction temperature	*cis* : *trans* ratio	Isolated yield
-15 °C to rt	>99 : 1	*cis*-**7**, 95%, >98% de
-20 °C	40 : 60	--
-78 °C	12 : 88	*trans*-**11**, 85%, >98% de

Scheme 1 *Reagents and conditions:* (i) ^{t}BuCOCl (1.0 eq), CH_2Cl_2, 4 Å molecular sieves, 16 h.

To confirm that the *cis*-diastereoisomer **7** was the thermodynamic product and the *trans*-diastereoisomer **11** was the kinetic product in this reaction, authentic samples of *cis*-**7** (>98% de) and *trans*-**11** (>98% de) were dissolved in CD_2Cl_2 and their interconversion at rt was monitored by ^{1}H NMR spectroscopic analysis. After 3.5 h, *trans*-**11** (>98% de) gave a 90 : 10 mixture of *cis*-**7** and *trans*-**11**, with complete conversion to *cis*-**7** (>98% de) observed after 24 h. Under the same conditions, *cis*-**7** remained unchanged, consistent with *trans*-**11** being the kinetic and *cis*-**7** the thermodynamic product in this reaction manifold. The interconversion of *trans*-**11** to *cis*-**7** is consistent with the half-life of *trans*-**11** being approximately 52 min under these conditions. At –20 °C in CD_2Cl_2 a significant decrease in the rate of isomerisation of *trans*-**11** to *cis*-**7** was noted, with the half-life of *trans*-**11** estimated at approximately 2.7 days. The influence of solvent upon the rate of conversion of *trans*-**11** to *cis*-**7** at rt was next established. In $C_6D_5CD_3$ the rate of conversion of *trans*-**11** to *cis*-**7** was significantly slowed, taking approximately 20 days to generate *cis*-**7** in >98% de (half-life ~ 5.2 days, Fig. 5).

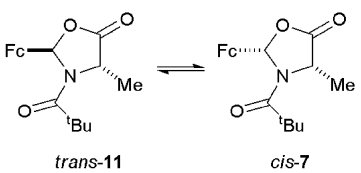


Fig. 5 Isomerisation of *trans*-**11** to *cis*-**7**.

The thermodynamic preference for the *cis*-diastereoisomer **7** in this reaction is not completely unexpected, since there is an established literature preference in related systems including five-membered ring acetals, oxazolidinones and imidazolidinones.[11] In an attempt to understand the origin of the thermodynamic preference for the *cis*-diastereoisomer in our system, *ab initio* calculations were performed at the HF/3-21G level for both *cis*-**7** and

trans-**11**. The minimum energy conformation of the oxazolidinone ring of *cis*-**7** indicates that an envelope conformation is preferred, which places the pivaloyl group on the face *anti*- to both the C(4)-methyl group and the ferrocenyl group (Fig. 6). This calculated conformation is remarkably similar to that observed for *cis*-**7** in the solid state.[10b] However, the *trans*-oxazolidinone **11** is predicted to adopt a planar ring conformation, which minimises any steric interaction between both the ferrocenyl group and the C(4)-methyl group with the *tert*-butyl group of the pivaloyl protecting group (Fig. 7).[12]

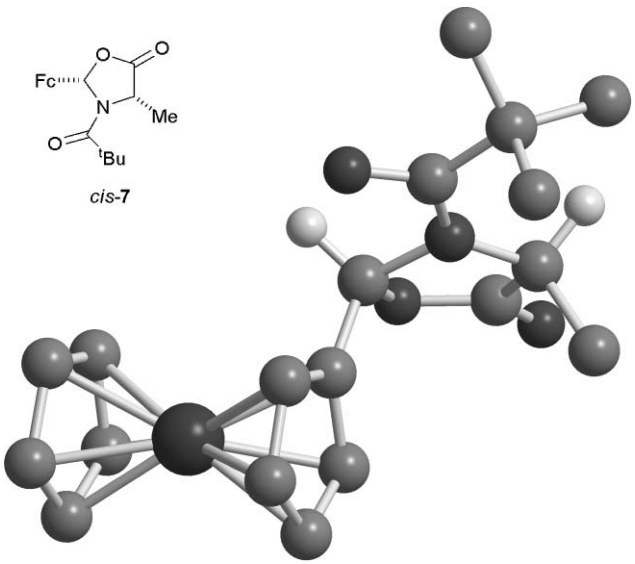


Fig. 6 Chem 3D representation of the minimum energy conformation for *cis*-**7** (some H atoms omitted for clarity).

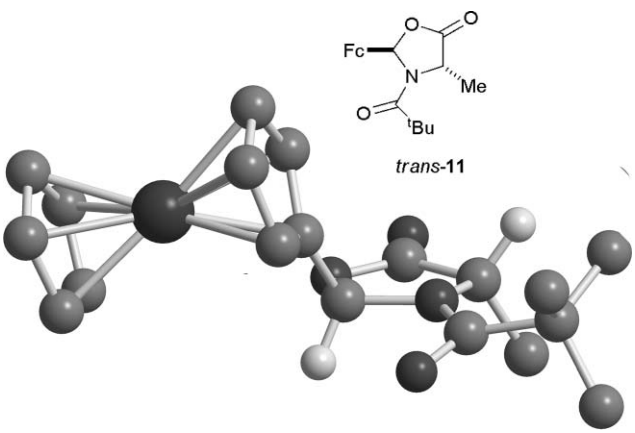
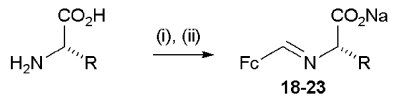


Fig. 7 Chem 3D representation of the minimum energy conformation for *trans*-**11** (some H atoms omitted for clarity).

Probing the generality of kinetic and thermodynamic control in ferrocenyl oxazolidinone formation

With kinetic and thermodynamic control for oxazolidinone formation from (*S*)-alanine delineated, the extension of this study to the stereoselective synthesis of a range of *cis*- and *trans*-oxazolidinones was investigated. (*S*)-2-Aminobutyric acid **12**, (*S*)-norvaline **13**, (*R*)-2-phenylglycine **14**, (*S*)-phenylalanine **15**, *O*-benzyl (*S*)-serine **16**, and (*S*)-tryptophan **17** were chosen as a representative set of α-amino acids for an investigation of this phenomenon. Following the literature protocol, imines **18–23** were synthesised from amino acids **12–17**, although a small amount of methanol had to be added to the reaction mixture in order to ensure homogeneity of the reacting species, giving imines **18–23** in >90% isolated yield (Scheme 2).



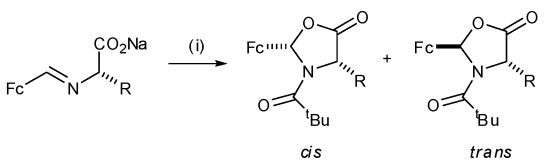
18-23

Amino acid	R	Imine	Yield (%)
12	Et	**18**	95
13	Pr	**19**	94
ent-**14**	Ph	*ent*-**20**	94
15	Bn	**21**	93
16	CH_2OBn	**22**	95
17	CH_2Ind*	**23**	94

* Ind = 3-indolyl

Scheme 2 *Reagents and conditions:* (i) NaOH (1.0 eq), MeOH, quant; (ii) FcCHO (1.05 eq), EtOH, MeOH, 4 Å molecular sieves, 16 h, rt.

Imines **18–23** were next subjected to cyclisation by treatment with pivaloyl chloride in CH_2Cl_2 in the presence of 4 Å molecular sieves at different temperatures, to yield the corresponding oxazolidinones **24–35** (Scheme 3). Analysis of these results indicates that, for each imine, cyclisation at −78 °C results in the corresponding *trans*-oxazolidinones **30–35** preferentially, giving *trans*-**30–35** in good yields and in >98% de after crystallisation from the crude reaction product. Intermediate *cis* : *trans* ratios were observed for the reactions performed at −20 °C, where the *trans*-oxazolidinone predominated in all cases except R = Ph. However, the *cis*-oxazolidinone was formed preferentially in high (96 : 4, R = CH_2OBn) to moderate (55 : 45, R = Bn) selectivity when the cyclisation was performed at −15 °C and allowed to warm to rt, giving the *cis*-diastereoisomers **24–29** in >98% de after crystallisation from the crude reaction product (Scheme 3).



R	T = -15 °C to rt *cis* : *trans*[a]	Yield (%)[b]	T = -20 °C *cis* : *trans*[a]	T = -78 °C *cis* : *trans*[a]	Yield (%)[b]
Me	>99:1	**7** 95 (>98)	40:60	12:88	**11** 85 (>98)
Et	88:12	**24** 52 (>98)	8:92	6:94	**30** 87 (>98)
Pr	88:12	**25** 43 (>98)	15:85	10:90	**31** 87 (>98)
Ph	88:12	***ent*-26** 37 (>98)	55:45	19:81	***ent*-32** 78 (>98)
Bn	55:45	**27** 40 (>98)	6:94	3:97	**33** 90 (>98)
CH_2OBn	96:4	**28** 54 (>98)	16:84	8:92	**34** 86 (>98)
CH_2Ind	85:15	**29** 47 (>98)	15:85	3:97	**35** 86 (>98)

Scheme 3 *Reagents and conditions:* (i) ^{t}BuCOCl (1.0 eq), CH_2Cl_2, 4 Å molecular sieves, 16 h. [a] *cis* : *trans* ratio determined by ^{1}H NMR spectroscopic analysis of the crude reaction product; [b] isolated yields (de in parentheses) of the major diastereoisomer after crystallisation from ether/pentane.

Mechanisms to account for the preferential formation of the *trans*-oxazolidinones as the kinetic products and the *cis*-oxazolidinones as the thermodynamic products in these reactions can be suggested. At low temperature, it may be postulated that reversible cyclisation of the imine carboxylates to the corresponding *trans*- or *cis*-oxazolidinone anions **36** or **37**, prior to irreversible acylation with pivaloyl chloride will generate the *trans*- and *cis*-oxazolidinones **38** and **39** respectively. Under these conditions, the formation of the *trans*-oxazolidinone anion, in which the 2-ferrocenyl and 4-alkyl or 4-aryl-substituent are *anti*- to each other, may be favoured, resulting in the preferential formation of the *trans*-oxazolidinone **38** after acylation (Fig. 8). Alternatively, formation of the *trans*-oxazolidinone anion **36** may occur much faster, with subsequent trapping *via* acylation affording **38** as the major product.

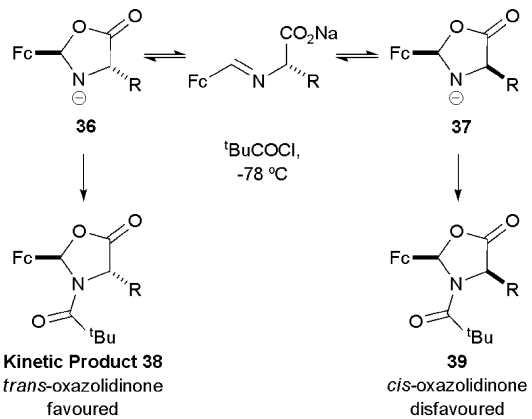


Fig. 8 Possible origin of kinetic control in oxazolidinone formation.

The preferential formation of the *cis*-oxazolidinone upon carrying out this reaction at higher temperatures reflects the preferred thermodynamic stability of the *cis*-oxazolidinone (*vide supra*). To account for this preference, a mechanism to allow equilibration from the *trans*- to the *cis*-oxazolidinone is required. Ring opening of either *trans* or *cis* oxazolidinones, **38** or **39** respectively, promoted by the 2-ferrocenyl substituent, will lead to the corresponding acyl-iminium intermediate. Assuming this mechanism, recyclisation of these acyl-iminium species must proceed *anti*- to the ferrocenyl group through either of the conformations **40** or **41**, with **41** leading to the thermodynamic *cis*-oxazolidinone **39** (Fig. 9).

Conclusions

In conclusion, the highly stereoselective preparation of a series of *cis*- and *trans*-2-ferrocenyl-3-pivaloyl-4-alkyl-1,3-oxazolidin-5-ones derived from ferrocenecarboxaldehyde and a range of α-amino acids, under thermodynamic or kinetic control, has been demonstrated. Synthetic applications of these enantiomerically pure *cis*- and *trans*-oxazolidinones as chiral auxiliaries are the subject of the following manuscript.[13]

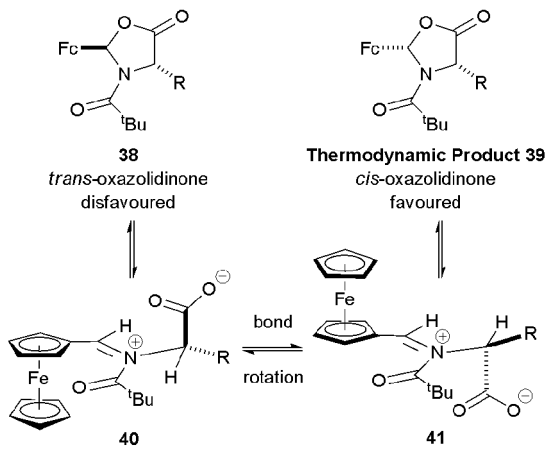


Fig. 9 Thermodynamic control in oxazolidinone formation.

Experimental

General

All reactions were performed under a nitrogen atmosphere. CH_2Cl_2 was distilled from CaH_2. THF and diethyl ether were distilled from sodium benzophenone ketyl. Methanol was distilled from $Mg(OMe)_2$. Ferrocenecarboxaldehyde was purchased from Aldrich or synthesised from ferrocene following known procedures.[14] Pivaloyl chloride was rendered HCl free by bubbling argon through it for ten minutes and subsequently distilled from $CaCl_2$.

Melting points (mp) were obtained using a Thermogalen™ III, Griffin Gallenkamp or Swiss Flawil melting point apparatus and are uncorrected.

Optical rotations were measured with a Perkin-Elmer 241 polarimeter with a thermally jacketted 10 cm cell. Concentrations (*c*) are given in g/100 mL and specific rotations [α] are given in units of 10^{-1} deg cm^2 g^{-1}.

Infrared spectra were recorded as KBr discs on a Perkin-Elmer 1750 FTIR spectrometer. Absorptions are recorded in wavenumbers (cm^{-1}). Only diagnostic peaks are quoted.

^{1}H NMR spectra were recorded at 200 MHz on a Varian Gemini 200 or a Bruker AC200 spectrometer, at 400 MHz on a Bruker AC400 spectrometer and at 500 MHz on a Bruker AM500 or AMX500 spectrometer. Chemical shifts (δ_H) are quoted in parts per million (ppm) downfield from tetramethylsilane and are referenced to the residual solvent peak. Coupling constants (*J*) were recorded in Hertz to the nearest 0.5 Hz. ^{13}C NMR spectra were recorded at 50.3 MHz on a Varian Gemini 200 or a Bruker AC200 spectrometer, at 100.6 MHz on a Bruker AC400 spectrometer and at 125.7 MHz on a Bruker AM500 or AMX500 spectrometer using DEPT editing. Chemical shifts (δ_C) are quoted in ppm downfield from tetramethylsilane and referenced to the corresponding deuterated solvent.

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, an APCI Platform or a Finnigan MAT95S spectrometer, with only molecular ions (M^+), fragments from molecular ions and major peaks being reported. Accurate mass analyses (HRMS) were performed on a VG AutoSpec spectrometer.

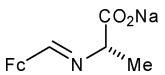
Microanalyses were performed on a Carlo Erba 1106 combustion elemental analyser.

Thin layer chromatography was performed on Merck aluminium sheets coated with 0.2 mm silica gel 60 F_{254}. Diastereomeric excesses were determined by ^{1}H NMR analysis of the crude reaction mixtures.

General procedure 1: preparation of imines 6, 18–23

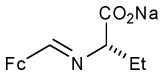
Aqueous NaOH (1.0 eq) was added to the corresponding α-amino acid (1.0 eq) and the resultant solution was stirred for 5 min at rt (a minimum amount of MeOH to aid dissolution was also added to the α-amino acids **14–17**). The solution was concentrated *in vacuo* and the residue was dried at 60 °C *in vacuo* for 16 h. 4 Å Molecular sieves, ferrocenecarboxaldehyde (1.05 eq) and absolute EtOH were added to the α-amino acid sodium salt (a minimum amount of MeOH to aid dissolution was also added in the case of α-amino acids salts of **14–17**) and the resultant mixture was stirred at rt for 5 h [for (*S*)-alanine] or for 16 h (for **12–17**); the course of the reaction was followed by IR spectroscopic analysis. The molecular sieves were removed by filtration and the filtrate was concentrated *in vacuo.* The residue was then suspended in pentane, filtered, washed with pentane, and dried *in vacuo* to yield the corresponding imines **6**, **12**–**17**.

Sodium (*S*)-2-[(ferrocenylmethylidene)amino]propanoate 6



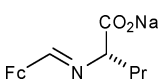
Following *general procedure 1*, (*S*)-alanine (1.0 g, 11.22 mmol), gave **6** as a yellow crystalline solid (3.28 g, 95%); mp 185–188 °C; $[\alpha]_D^{21}$ −36.1 (*c* 0.2 in MeOH); ν_{max} (KBr) 2969, 2872 (C–H), 1641 (C=O), 1587 (C=N), 1397; δ_H (200 MHz, CD_3OD) 1.41 (3H, d, *J* 7.0, C(3)H_3), 3.86 (1H, q, *J* 7.0, C(2)*H*), 4.21 (5H, s, *Cp′*), 4.29–4.99 (4H, m, *Cp*), 8.17 (1H, br s, C*H*N); δ_C (50.3 MHz, CD_3OD) 20.5 (*C*(3)H_3), 69.3, 69.8, 71.4, 71.8 (*C*(2), 4 × *Cp*, 5 × *Cp′*), 80.4 (1 × *Cp*), 162.5 (*C*N), 178.1 (*C*(1)); *m*/*z* (FAB$^+$) 330 ([M + Na]$^+$, 100%), 308 ([M + H]$^+$, 97), 286 ([M − Na + 2H]$^+$, 53).

Sodium (*S*)-2-[(ferrocenylmethylidene)amino]butanoate 18



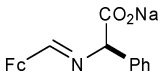
Following *general procedure 1*, (*S*)-2-aminobutyric acid **12** (2.60 g, 25.20 mmol) gave **18** as an orange crystalline solid (7.69 g, 95%); mp 212–214 °C; $[\alpha]_D^{24}$ +36.4 (*c* 0.3 in MeOH); ν_{max} (KBr) 3078, 2960, 2926, 2871 (C–H), 1642 (C=O), 1594 (C=N), 1412, 1400, 1386; δ_H (400 MHz, CD_3OD) 0.93 (3H, t, *J* 7.0, C(4)H_3), 1.73–1.83 (1H, m, C(3)H_AH_B), 1.90–2.00 (1H, m, C(3)H_AH_B), 3.55–3.62 (1H, m, C(2)*H*), 4.21 (5H, s, *Cp′*), 4.30–4.88 (4H, m, *Cp*), 8.16 (1H, br s, C*H*N); δ_C (50.3 MHz, CD_3OD) 9.4 (*C*(4)H_3), 25.8 (*C*(3)H_2), 67.5, 68.1, 68.3, 69.7 (4 × *Cp*, 5 × *Cp′*), 77.7 (*C*(2)H), 79.0 (1 × *Cp*), 162.4 (*C*N), 178.2 (*C*(1)); *m*/*z* (FAB$^+$) 344 ([M + Na]$^+$, 12%), 322 ([M + H]$^+$, 64).

Sodium (*S*)-2-[(ferrocenylmethylidene)amino]pentanoate 19



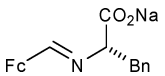
Following *general procedure 1*, (*S*)-norvaline **13** (1.17 g, 9.99 mmol) gave **19** as an orange crystalline solid (3.16 g, 94%); mp 228–230 °C; $[\alpha]_D^{24}$ +65.0 (*c* 0.3 in MeOH); ν_{max} (KBr) 3096, 2956, 2932, 2861 (C–H), 1640 (C=O), 1594 (C=N), 1410; δ_H (200 MHz, CD_3OD) 0.96 (3H, t, *J* 7.0, C(5)H_3), 1.25–1.39 (2H, m, C(4)H_2), 1.73–1.93 (2H, m, C(3)H_2), 3.66–3.80 (1H, m, C(2)*H*), 4.21 (5H, s, *Cp′*), 4.29–4.88 (4H, m, *Cp*), 8.16 (1H, br s, C*H*N); δ_C (50.3 MHz, CD_3OD) 12.7 (*C*(5)), 19.3 (*C*(4)), 35.6 (*C*(3)), 68.1, 69.1, 69.5, 70.4 (4 × *Cp*), 68.8 (5 × *Cp′*), 76.3 (*C*(2)), 79.8 (1 × *Cp*), 163.1 (*C*N), 179.0 (*C*(1)); *m*/*z* (FAB$^+$) 358 ([M + Na]$^+$, 13%), 336 ([M + H]$^+$, 48).

Sodium (*R*)-2-[(ferrocenylmethylidene)amino]-2-phenyl-ethanoate *ent*-20



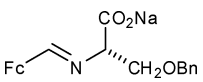
Following *general procedure 1*, (*R*)-2-phenylglycine *ent*-**14** (1.94 g, 12.83 mmol), gave *ent*-**20** as an orange crystalline solid (4.45 g, 94%); mp 217–220 °C; $[\alpha]_D^{24}$ −167 (*c* 0.2 in MeOH); ν_{max} (KBr) 3088, 3054, 2879 (C–H), 1636 (C=O), 1599 (C=N), 1378; δ_H (200 MHz, CD_3OD) 4.10–4.18 (4H, m, *Cp*), 4.29–4.39 (5H, m, *Cp′*), 4.70–4.99 (1H, m, C(2)*H*), 7.22–7.57 (5H, m, *Ph*), 8.21–8.27 (1H, br s, C*H*N); δ_C (100.6 MHz, CD_3OD) 69.6, 70.7, 71.8, 71.9 (4 × *Cp*), 70.1 (5 × *Cp′*), 74.9 (*C*(2)), 81.3 (1 × *Cp*), 128.0, 129.1, 129.3 (*o*,*m*,*p*-*Ph*), 142.8 (*i*-*Ph*), 164.4 (*C*N), 178.7 (*C*(1)); *m*/*z* (FAB$^+$) 370 ([M + H]$^+$, 19%), 348 ([M − Na + 2H]$^+$, 100).

Sodium (*S*)-2-benzyl-2-[(ferrocenylmethylidene)amino]-ethanoate 21



Following *general procedure 1*, (*S*)-phenylalanine **15** (2.12 g, 12.83 mmol), gave **21** as a brown crystalline solid (4.57 g, 93%); mp 255–256 °C (dec); $[\alpha]_D^{24}$ +214 (*c* 0.1 in MeOH); ν_{max} (KBr) 3087, 3024, 2874 (C–H), 1643 (C=O), 1600 (C=N), 1383, 701; δ_H (200 MHz, CD_3OD) 3.95–3.98 (4H, m, *Cp*), 4.29–4.37 (5H, m, *Cp′*), 4.57–4.93 (3H, m, C(2)*H*, CH_2Ph), 7.05–7.42 (5H, m, *Ph*), 7.93 (1H, br s, C*H*N); δ_C (100.6 MHz, CD_3OD) 41.2 (*C*H_2Ph), 68.9, 70.9, 71.9, 72.1 (4 × *Cp*), 70.3 (5 × *Cp′*), 74.8 (*C*(2)), 80.3 (1 × *Cp*), 127.2, 129.4, 130.6 (*o*,*m*,*p*-*Ph*), 141.0 (*i*-*Ph*), 165.3 (*C*N), 179.0 (C(1)); *m*/*z* (FAB$^+$) 384 ([M + H]$^+$, 9%), 362 ([M − Na + 2H]$^+$, 100).

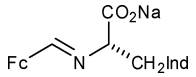
Sodium (*S*)-2-benzyloxymethyl-2-[(ferrocenyl-methylidene)amino]ethanoate 22



Following *general procedure 1*, *O*-benzyl-(*S*)-serine **16** (1.98 g, 10.14 mmol), gave **22** as an orange crystalline solid (3.99 g, 95%); mp 188–190 °C (dec); $[\alpha]_D^{23}$ +108 (*c* 0.3 in MeOH); ν_{max} (KBr) 3087, 3028, 2867 (C–H), 1643 (C=O), 1600 (C=N), 1412, 1106; δ_H (200 MHz, CD_3OD) 3.82–4.99 (14H, m, *Cp*, *Cp′*, C*H*CH_2OCH_2Ph), 7.20–7.32 (5H, m, *Ph*), 8.14 (1H, br s, C*H*N); δ_C (100.6 MHz, CD_3OD) 69.3, 70.8, 71.7, 71.9 (4 × *Cp*), 70.3 (5 × *Cp′*), 73.4, 74.1 (CH_2OCH_2), 77.7 (*C*(2)), 80.9 (1 × *Cp*), 128.6, 129.0, 129.3 (*o*,*m*,*p*-*Ph*), 139.7 (*i*-*Ph*), 165.6 (*C*N), 177.4 (*C*(1));

m/z (FAB$^+$) 436 ([M + Na]$^+$, 28%), 414 ([M + H]$^+$, 57), 392 ([M – Na + 2H]$^+$, 100), 91 ([C_7H_7]$^+$, 34).

Sodium (*S*)-2-[(ferrocenylmethylidene)amino]-3-(3′-indolyl)propanoate 23

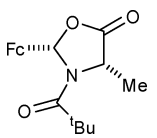


Following *general procedure 1*, (*S*)-tryptophan **17** (1.29 g, 6.32 mmol), gave **23** as a brown crystalline solid (2.51 g, 94%); mp 180–183 °C; $[\alpha]_D^{22}$ +275 (*c* 0.2 in MeOH); ν_{max} (KBr) 3412 (N–H), 3096, 2968, 2870 (C–H), 1636 (C=O), 1587 (C=N), 1394, 740; δ_H (200 MHz, CD_3OD) 4.10–4.94 (12H, m, C(2)*H*, C(3)H_2, *Cp*′, *Cp*), 6.98–7.73 (5H, m, *Ar*), 7.84 (1H, br s, C*H*N); δ_C (125.7 MHz, CD_3OD) 31.0 (*C*(3)), 68.6, 70.8, 71.0, 71.6, 71.8 (*C*(2), 4 × *Cp*), 70.1 (5 × *Cp*′), 80.5 (1 × *Cp*), 112.3, 119.5, 119.7, 122.2, 124.2 (5 × *Ar*), 113.5, 129.0, 138.2 (3 × *Ar*), 164.7 (*C*N), 179.7 (*C*(1)); *m/z* (FAB$^+$) 445 ([M + Na]$^+$, 34%), 423 ([M + H]$^+$, 45), 401 ([M – Na + 2H]$^+$, 100).

General procedure 2: cyclisation of imines 6, 18–23 to oxazolidinones 7, 11, 24–35

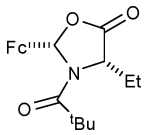
4 Å Molecular sieves and the corresponding imine (1.0 eq) were suspended in CH_2Cl_2. For *cis*-oxazolidinones, the resultant mixture was cooled to −15 °C. A solution of pivaloyl chloride (1.0 eq) in CH_2Cl_2 was added dropwise and the reaction mixture was allowed to warm to rt over 16 h, and then filtered. For *trans*-oxazolidinones, the resultant mixture was cooled to −78 °C. A solution of pivaloyl chloride (1.0 eq) in CH_2Cl_2 was added dropwise and the reaction mixture was stirred at −78 °C for 16 h, allowed to warm to rt over 5 min, and then filtered. The filtrate was then concentrated *in vacuo*; it is important not to overheat the solution in order to prevent possible racemisation. Several portions of Et_2O were added and the mixture was then passed through a short plug of celite and silica (eluent Et_2O). The filtrate was concentrated *in vacuo* (avoiding strong heating), and the residue was purified by recrystallisation from Et_2O/pentane.

(2*S*,4*S*)-2-Ferrocenyl-3-pivaloyl-4-methyl-1,3-oxazolidin-5-one 7[10]



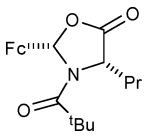
Following *general procedure 2*, imine **6** (3.0 g, 9.77 mmol) gave **7** as a yellow crystalline solid (3.42 g, 95%, >98% de); $C_{19}H_{23}FeNO_3$ requires C, 61.8; H, 6.3; N, 3.8%; found C, 62.0; H, 6.0; N, 3.5%; mp 104–105 °C; $[\alpha]_D^{21}$ +24.3 (*c* 0.9 in $CHCl_3$); ν_{max} (KBr) 3099, 2979, 2962 (C–H), 1785 (OC=O), 1646 (NC=O), 1350, 1194; δ_H (200 MHz, $CDCl_3$) 1.27 (9H, s, C(CH_3)$_3$), 1.56 (3H, d, *J* 7.0, C(4)CH_3), 4.18–4.60 (4H, m, *Cp*), 4.25 (5H, s, *Cp*′), 4.64 (1H, q, *J* 7.0, C(4)*H*), 7.07 (1H, s, C(2)*H*); δ_C (50.3 MHz, $CDCl_3$) 20.1 (C(4)*C*H$_3$), 28.1 (C(*C*H$_3$)$_3$), 39.9 (*C*(CH$_3$)$_3$), 52.0 (*C*(4)H), 65.2, 67.8, 68.4, 69.2 (*C*(2), 4 × *Cp*, 5 × *Cp*′), 84.9 (1 × *Cp*), 173.6, 175.8 (*C*(5), N*C*O); *m/z* (EI$^+$) 369 ([M]$^+$, 31%), 240 ([M – C_4H_9CO – CO_2]$^+$, 39), 57 ([C_4H_9]$^+$, 100).

(2*S*,4*S*)-2-Ferrocenyl-3-pivaloyl-4-ethyl-1,3-oxazolidin-5-one 24



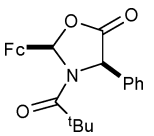
Following *general procedure 2*, imine **18** (0.98 g, 3.05 mmol) gave **24** as a pale orange crystalline solid (0.61 g, 52%, >98% de); $C_{20}H_{25}FeNO_3$ requires C, 62.7; H, 6.6; N, 3.65%; found C, 62.6; H, 6.4; N, 3.5%; mp 119–122 °C; $[\alpha]_D^{23}$ +42.0 (*c* 0.9 in $CHCl_3$); ν_{max} (KBr) 2974 (C–H), 1780 (OC=O), 1652 (NC=O), 1176; δ_H (500 MHz, $CDCl_3$) 1.10 (3H, t, *J* 7.5, CH_2CH_3), 1.27 (9H, s, C(CH_3)$_3$), 1.80–1.89 (2H, m, CH_2CH$_3$), 4.17–4.26 (2H, m, *Cp*), 4.58–4.59 (2H, m, *Cp*), 4.25 (5H, s, *Cp*′), 4.37 (1H, dd, *J* 10.5, 4.5, C(4)*H*), 7.04 (1H, s, C(2)*H*); δ_C (50.3 MHz, $CDCl_3$) 10.0 (CH_2CH_3), 27.9 (C(*C*H$_3$)$_3$), 28.0 (*C*H$_2$CH$_3$), 39.9 (*C*(CH$_3$)$_3$), 56.9 (*C*(4)), 65.7, 67.8, 68.4, 69.2 (*C*(2), 4 × *Cp*, 5 × *Cp*′), 85.0 (1 × *Cp*), 88.6 (*C*(2)), 172.6, 176.2 (*C*(5), N*C*O); *m/z* (APCI$^+$) 384 ([M + H]$^+$, 100%), 254 ([M – C_4H_9CO – CO_2]$^+$, 14), 215 ([FcCHO + H]$^+$, 7).

(2*S*,4*S*)-2-Ferrocenyl-3-pivaloyl-4-propyl-1,3-oxazolidin-5-one 25



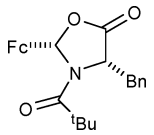
Following *general procedure 2*, imine **19** (3.16 g, 9.43 mmol) gave **25** as a pale brown crystalline solid (1.61 g, 43%, >98% de); $C_{21}H_{27}FeNO_3$ requires C, 63.5; H, 6.85; N, 3.5%; found C, 63.5; H, 6.7; N, 3.4%.; mp 79–81 °C; $[\alpha]_D^{23}$ +31.0 (*c* 0.2 in $CHCl_3$); ν_{max} (KBr) 3086, 2959, 2877 (C–H), 1790 (OC=O), 1629 (NC=O), 1361, 1173; δ_H (200 MHz, $CDCl_3$) 0.93 (3H, t, *J* 7.0, $CH_2CH_2CH_3$), 1.27 (9H, s, C(CH_3)$_3$), 1.43–1.85 (4H, m, CH_2CH_2CH$_3$), 4.19–4.29 (2H, m *Cp*), 4.58–4.59 (2H, m, *Cp*), 4.25 (5H, s, *Cp*′), 4.47 (1H, dd, *J* 9.5, 4.0, C(4)*H*), 7.06 (1H, s, C(2)*H*); δ_C (50.3 MHz, $CDCl_3$) 13.5 (CH_2CH_3), 18.8 (*C*H$_2$CH$_3$), 27.9 (C(*C*H$_3$)$_3$), 36.5 (*C*(4)H$_2$), 39.8 (*C*(CH$_3$)$_3$), 55.6 (*C*(4)), 65.8, 67.6, 68.4, 69.0 (4 × *Cp*), 69.2 (5 × *Cp*′), 85.1 (1 × *Cp*), 88.6 (*C*(2)), 172.7, 176.2 (*C*(5), N*C*O); *m/z* (APCI$^+$) 398 ([M + H]$^+$, 100%).

(2*R*,4*R*)-2-Ferrocenyl-3-pivaloyl-4-phenyl-1,3-oxazolidin-5-one *ent*-26



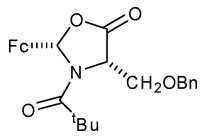
Following *general procedure 2*, *ent*-**20** (2.40 g, 6.50 mmol) gave *ent*-**26** as a brown oil (1.04 g, 37%, >98% de); $[\alpha]_D^{23}$ −18.8 (*c* 0.1 in $CHCl_3$); ν_{max} (KBr) 3094, 2971, 2873 (C–H), 1791 (OC=O), 1651 (NC=O), 1355, 1171; δ_H (500 MHz, $CDCl_3$) 1.05 (9H, s, C(CH_3)$_3$), 3.87–4.24 (4H, m, *Cp*), 4.18 (5H, s, *Cp*′), 5.67 (1H, s, C(4)*H*), 7.14–7.22 (6H, m, C(2)*H*, *Ph*); δ_C (125.7 MHz, $CDCl_3$) 27.7 (C(*C*H$_3$)$_3$), 39.8 (*C*(CH$_3$)$_3$), 59.6 (*C*(4)), 65.9, 67.3, 68.7, 69.2 (4 × *Cp*), 68.8 (5 × *Cp*′), 83.6 (1 × *Cp*), 89.2 (*C*(2)), 126.2, 128.1 (*o*,*m*,*p*-*Ph*), 134.5 (*i*-*Ph*), 170.4, 176.5 (*C*(5), N*C*O); *m/z* (APCI$^+$) 432 ([M + H]$^+$, 100%); HRMS (CI)$^+$ $C_{24}H_{25}FeNO_3^+$ ([M]$^+$) requires 431.1183; found 431.1172.

(2*S*,4*S*)-2-Ferrocenyl-3-pivaloyl-4-benzyl-1,3-oxazolidin-5-one 27



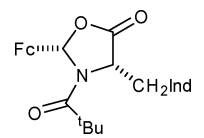
Following *general procedure 2*, imine **21** (2.61 g, 6.81 mmol) gave **27** as brown oil (1.20 g, 40%, >98% de); δ_H (500 MHz, $CDCl_3$) 1.25 (9H, s, C(CH_3)$_3$), 3.09 (1H, dd, *J* 14.5, 5.0, CH_AH_BPh), 3.14 (1H, dd, *J* 14.5, 9.0, CH_AH_BPh), 4.08–4.34 (4H, m, *Cp*), 4.26 (5H, s, *Cp′*), 4.81 (1H, dd, *J* 9.0, 5.0, C(4)*H*), 7.08 (1H, s, C(2)*H*), 7.18–7.32 (5H, m, *Ph*); δ_C (125.7 MHz, $CDCl_3$) 28.0 (C(CH_3)$_3$), 39.7 (C(4)CH_2), 39.8 ($C(CH_3)_3$), 56.8 (*C*(4)), 65.7, 67.7, 68.3, 69.1 (4 × *Cp*), 69.0 (5 × *Cp′*), 85.0 (1 × *Cp*), 88.4 (*C*(2)), 127.1, 128.4, 129.2 (*o*,*m*,*p*-*Ph*), 135.0 (*i*-*Ph*), 171.2, 176.0 (*C*(5), N*C*O); *m*/*z* (APCI$^+$) 446 ([M + H]$^+$, 100%); HRMS (CI$^+$) $C_{25}H_{28}FeNO_3^+$ ([M + H]$^+$) requires 446.1418; found 446.1414.

(2*S*,4*S*)-2-Ferrocenyl-3-pivaloyl-4-benzyloxymethyl-1,3-oxazolidin-5-one 28



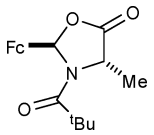
Following *general procedure 2*, imine **22** (3.46 g, 8.37 mmol) gave **28** as a brown oil (2.16 g, 54%, >98% de); ν_{max} (KBr) 2968 (C–H), 1798 (OC=O), 1644 (NC=O), 1353, 1249, 1176, 1106; δ_H (500 MHz, $CDCl_3$) 1.18 (9H, s, C(CH_3)$_3$), 3.74 (2H, d, *J* 4.5, C(4)CH_2), 4.06–4.07 (1H, m, *Cp*), 4.16–4.17 (1H, m, *Cp*), 4.26–4.30 (2H, m, *Cp*), 4.22 (5H, s, *Cp′*), 4.47 (2H, s, CH_2Ph), 4.75 (1H, t, *J* 4.5, C(4)*H*), 7.00 (1H, s, C(2)*H*), 7.19–7.34 (5H, m, *Ph*); δ_C (125.7 MHz, $CDCl_3$) 27.8 (C(CH_3)$_3$), 39.9 ($C(CH_3)_3$), 56.6 (*C*(4)), 66.2, 67.5, 68.5, 68.7 (4 × *Cp*), 68.9 (5 × *Cp′*), 69.3, 72.9 (CH_2OCH_2), 84.1 (1 × *Cp*), 89.1 (*C*(2)), 127.6, 127.8, 128.1 (*o*,*m*,*p*-*Ph*), 136.6 (*i*-*Ph*), 170.5, 176.2 (*C*(5), N*C*O); *m*/*z* (FAB$^+$) 476 ([M + H]$^+$, 79%), 475 ([M]$^+$, 100), 91 ([C_7H_7]$^+$, 97), 57 ([C_4H_9]$^+$, 75); HRMS (FAB$^+$) $C_{26}H_{30}FeNO_4^+$ ([M + H]$^+$) requires 476.1524; found 476.1502.

(2*S*,4*S*)-2-Ferrocenyl-3-pivaloyl-4-(3′-indolylmethyl)-1,3-oxazolidin-5-one 29



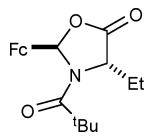
Following *general procedure 2*, imine **23** (1.11 g, 2.63 mmol) gave **29** as a brown oil (0.60 g, 47%, >98% de); δ_H (500 MHz, $CDCl_3$) 1.25 (9H, s, C(CH_3)$_3$), 3.28 (1H, dd, *J* 15.5, 4.5, C(4)CH_AH_B), 3.34 (1H, dd, *J* 15.5, 9.0, C(4)CH_AH_B), 4.14–4.29 (4H, m, *Cp*), 4.25 (5H, s, *Cp′*), 4.88 (1H, dd, *J* 9.0, 4.5, C(4)*H*), 7.09–7.14 (3H, m, C(2)*H*, 2 × *Ar*), 7.19 (1H, t, *J* 8.0, *Ar*), 7.35–7.50 (2H, m, *Ar*), 8.23 (1H, br s, N*H*); δ_C (125.7 MHz, $CDCl_3$) 28.2 (C(CH_3)$_3$), 30.1 (C(4)CH_2), 40.1 ($C(CH_3)_3$), 56.6 (*C*(4)H), 65.8, 67.7, 68.5, 69.6 (4 × *Cp*), 69.2 (5 × *Cp′*), 85.1 (1 × *Cp*), 88.7 (*C*(2)), 109.4, 127.2, 135.8, 111.2, 118.4, 119.6, 122.1, 123.6 (8 × *Ar*), 172.1, 176.4 (*C*(5), N*C*O); *m*/*z* (APCI$^+$) 485 ([M + H]$^+$, 100%); HRMS (CI$^+$) $C_{27}H_{29}FeN_2O_3^+$ ([M + H]$^+$) requires 485.1527; found 485.1535.

(2*R*,4*S*)-2-Ferrocenyl-3-pivaloyl-4-methyl-1,3-oxazolidin-5-one 11



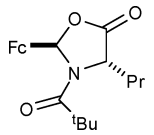
Following *general procedure 2*, imine **6** (1.70 g, 5.54 mmol) gave **11** as a yellow crystalline solid (1.74 g, 85%, >98% de); mp 130–131 °C; $[\alpha]_D^{24}$ +282 (*c* 0.2 in $CHCl_3$); ν_{max} (KBr) 3002, 2967 (C–H), 1786 (OC=O), 1622 (NC=O), 1363, 1248; δ_H (500 MHz, $CDCl_3$) 1.12 (9H, s, C(CH_3)$_3$), 1.59 (3H, d, *J* 7.0, C(4)CH_3), 4.07–4.45 (4H, m, *Cp*), 4.25 (5H, s, *Cp′*), 4.62 (1H, q, *J* 7.0, C(4)*H*), 6.67 (1H, s, C(2)*H*); δ_C (125.7 MHz, $CDCl_3$) 20.1 (C(4)CH_3), 28.2 (C(CH_3)$_3$), 41.0 ($C(CH_3)_3$), 53.2 (*C*(4)), 65.4, 68.2, 68.4, 69.5 (4 × *Cp*), 69.2 (5 × *Cp′*), 86.5 (1 × *Cp*), 88.2 (*C*(2)), 173.3, 179.5 (*C*(5), N*C*O); *m*/*z* (APCI$^+$) 370 ([M + H)$^+$, 100%), 215 ([FcCHO + H]$^+$, 23); HRMS (CI$^+$) $C_{19}H_{24}FeNO_3^+$ ([M + H]$^+$) requires 370.1105; found 370.1111.

(2*R*,4*S*)-2-Ferrocenyl-3-pivaloyl-4-ethyl-1,3-oxazolidin-5-one 30



Following *general procedure 2*, imine **12** (120 mg, 0.37 mmol) gave **30** as a pale yellow crystalline solid (125 mg, 87%, >98% de); mp 143–144 °C; $[\alpha]_D^{23}$ +281 (*c* 0.2 in $CHCl_3$); ν_{max} (KBr) 3092, 2974 (C–H), 1781 (OC=O), 1621 (NC=O), 1362, 1188; δ_H (500 MHz, $CDCl_3$) 0.95 (3H, t, *J* 7.5, CH_2CH_3), 1.13 (9H, s, C(CH_3)$_3$), 2.00 (1H, dqd, *J* 15.0, 7.5, 2.5, C(4)CH_AH_B), 2.18 (1H, dqd, *J* 15.0, 7.5, 6.0, C(4)CH_AH_B), 4.12–4.47 (4H, m, *Cp*), 4.26 (5H, s, *Cp′*), 4.64 (1H, dd, *J* 6.0, 2.5, C(4)*H*), 6.65 (1H, s, C(2)*H*); δ_C (125.7 MHz, $CDCl_3$) 7.8 (CH_2CH_3), 25.5 (CH_2CH_3), 28.3 (C(CH_3)$_3$), 41.0 ($C(CH_3)_3$), 58.1 (*C*(4)), 65.3, 68.2, 68.4, 69.7 (4 × *Cp*), 69.2 (5 × *Cp′*), 86.6 (1 × *Cp*), 88.8 (*C*(2)), 172.6, 179.3 (*C*(5), N*C*O); *m*/*z* (APCI$^+$) 384 ([M + H]$^+$, 100%); HRMS (CI$^+$) $C_{20}H_{26}FeNO_3^+$ ([M + H]$^+$) requires 384.1262; found 384.1259.

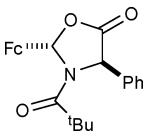
(2*R*,4*S*)-2-Ferrocenyl-3-pivaloyl-4-propyl-1,3-oxazolidin-5-one 31



Following *general procedure 2*, imine **13** (1.21 g, 3.61 mmol) gave **31** as a yellow crystalline solid (1.25 g, 87%, >98% de); mp 103–108 °C; $[\alpha]_D^{25}$ +294 (*c* 0.1 in $CHCl_3$); ν_{max} (KBr) 3100, 2975, 2937 (C–H), 1783 (OC=O), 1628 (NC=O), 1223, 1188; δ_H (500 MHz, $CDCl_3$) 0.96 (3H, t, *J* 7.5, CH_2CH_3), 1.12 (9H, s, C(CH_3)$_3$), 1.29–1.37 (1H, m, $CH_AH_BCH_3$), 1.40–1.48 (1H, m, $CH_AH_BCH_3$), 1.88–1.94 (1H, m, C(4)CH_AH_B), 2.05–2.12 (1H, m, C(4)CH_AH_B), 4.12–4.30 (2H, m, *Cp*), 4.44–4.47 (2H, m, *Cp*), 4.26 (5H, s, *Cp′*), 4.64 (1H, dd, *J* 6.5, 2.5, C(4)*H*), 6.63 (1H, s, C(2)*H*); δ_C (125.7 MHz, $CDCl_3$) 13.8 (CH_2CH_3), 17.0 (CH_2CH_3), 28.3 (C(CH_3)$_3$), 34.5 (C(4)CH_2), 41.1 ($C(CH_3)_3$), 57.4 (*C*(4)H), 65.3, 68.2, 68.3, 69.7 (4 × *Cp*), 69.2 (5 × *Cp′*), 86.5 (1 × *Cp*), 88.8 (*C*(2)), 172.7, 179.5 (*C*(5), N*C*O); *m*/*z* (APCI$^+$) 398 ([M + H]$^+$, 100%), 354 ([M – C_3H_7]$^+$, 32);

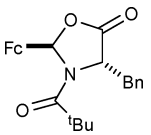
HRMS (CI$^+$) $C_{21}H_{28}FeNO_3^+$ ([M + H]$^+$) requires 398.1418; found 398.1402.

(2*S*,4*R*)-2-Ferrocenyl-3-pivaloyl-4-phenyl-1,3-oxazolidin-5-one *ent*-32



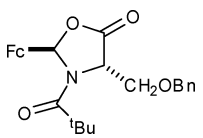
Following *general procedure 2*, imine *ent*-**14** (1.07 g, 2.90 mmol) gave *ent*-**32** as a yellow crystalline solid (0.97 g, 78%, >98% de); $C_{24}H_{25}FeNO_3$ requires C, 66.8; H, 5.8; N, 3.25%; found C, 66.9; H, 5.9; N, 3.15%; mp 176–179 °C; $[\alpha]_D^{25}$ –182 (*c* 0.2 in $CHCl_3$); ν_{max} (KBr) 2966 (C–H), 1783 (OC=O), 1626 (NC=O), 1351, 1183; δ_H (500 MHz, $CDCl_3$) 0.91 (9H, s, C(CH_3)$_3$), 4.18–4.22 (2H, m, *Cp*), 4.61–4.62 (2H, m, *Cp*), 4.28 (5H, s, *Cp′*), 5.52 (1H, s, C(4)*H*), 7.06 (1H, s, C(2)*H*), 7.34–7.46 (5H, m, *Ph*); δ_C (125.7 MHz, $CDCl_3$) 27.8 (C(*C*H$_3$)$_3$), 40.7 (*C*(CH$_3$)$_3$), 61.7 (*C*(4)), 64.6, 68.2, 68.4, 70.1 (4 × *Cp*), 69.1 (5 × *Cp′*), 85.1 (1 × *Cp*), 90.3 (*C*(2)), 126.2, 129.2, 129.5 (*o*,*m*,*p*-*Ph*), 137.9 (*i*-*Ph*), 170.5, 179.5 (*C*(5), N*C*O); *m*/*z* (APCI$^+$) 432 ([M + H]$^+$, 100%).

(2*R*,4*S*)-2-Ferrocenyl-3-pivaloyl-4-benzyl-1,3-oxazolidin-5-one 33



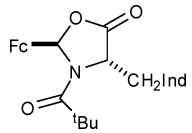
Following *general procedure 2*, imine **15** (170 mg, 0.44 mmol) gave **33** as a yellow crystalline solid (178 mg, 90%, >98% de); $C_{25}H_{27}FeNO_3$ requires C, 67.4; H, 6.1; N, 3.15%; found C, 67.5; H, 6.1; N, 3.1%; mp 117–119 °C; $[\alpha]_D^{23}$ +283 (*c* 0.2 in $CHCl_3$); ν_{max} (KBr) 2992, 2959, 2928 (C–H), 1790 (OC=O), 1623 (NC=O), 1368, 702; δ_H (400 MHz, $CDCl_3$) 0.96 (9H, s, C(CH_3)$_3$), 3.26 (1H, dd, *J* 14.0, 2.0, C(4)CH_AH$_B$), 3.50 (1H, dd, *J* 14.0, 6.0, C(4)CH$_A$$H_B$), 4.10–4.33 (4H, m, *Cp*), 4.21 (5H, s, *Cp′*), 4.90 (1H, dd, *J* 6.0, 2.0, C(4)*H*), 6.05 (1H, s, C(2)*H*), 7.11–7.31 (5H, m, *Ph*); δ_C (100.6 MHz, $CDCl_3$) 28.0 (C(*C*H$_3$)$_3$), 35.9 (C(4)*C*H$_2$), 40.7 (*C*(CH$_3$)$_3$), 58.6 (*C*(4)H), 65.8, 68.0, 68.5, 69.6 (4 × *Cp*), 69.2 (5 × *Cp′*), 87.4 (1 × *Cp*), 88.2 (*C*(2)), 127.2, 128.4, 129.8 (*o*,*m*,*p*-*Ph*), 134.9 (*i*-*Ph*), 171.9, 178.6 (*C*(5), N*C*O); *m*/*z* (APCI$^+$) 446 ([M + H]$^+$, 100%).

(2*R*,4*S*)-2-Ferrocenyl-3-pivaloyl-4-benzyloxymethyl-1,3-oxazolidin-5-one 34



Following *general procedure 2*, imine **16** (185 mg, 0.45 mmol) gave **34** as a yellow crystalline solid (184 mg, 86%, >98% de); $C_{26}H_{29}NO_4Fe$ requires C, 65.7; H, 6.15; N, 2.95%; found C, 65.5; H, 6.1; N, 2.9%; mp 111–113 °C; $[\alpha]_D^{25}$ +205 (*c* 0.1 in $CHCl_3$); ν_{max} (KBr) 2972, 2872 (C–H), 1793 (OC=O), 1627 (NC=O), 1371, 1350; δ_H (500 MHz, $CDCl_3$) 1.05 (9H, s, C(CH_3)$_3$), 3.89 (1H, dd, *J* 10.0, 2.0, C(4)CH_AH$_B$), 3.94 (1H, dd, *J* 10.0, 2.0, C(4)CH$_A$$H_B$), 4.14–4.27 (4H, m, *Cp*), 4.26 (5H, s, *Cp′*), 4.51 (1H, d, *J* 12.0, CH_AH$_B$Ph), 4.60 (1H, d, *J* 12.0, CH$_A$$H_B$Ph), 4.69 (1H, t, *J* 2.0, C(4)*H*), 6.68 (1H, s, C(2)*H*), 7.27–7.37 (5H, m, *Ph*); δ_C (125.7 MHz, $CDCl_3$) 28.2 (C(*C*H$_3$)$_3$), 40.9 (*C*(CH$_3$)$_3$), 58.8 (*C*(4)), 65.3, 68.1, 68.2, 70.0 (4 × *Cp*), 69.1 (5 × *Cp′*), 69.5, 73.4 (*C*H$_2$O*C*H$_2$), 84.2 (1 × *Cp*), 89.6 (*C*(2)), 127.6, 127.8, 128.4 (*o*,*m*,*p*-*Ph*), 137.1 (*i*-*Ph*), 171.0, 179.2 (*C*(5), N*C*O); *m*/*z* (APCI$^+$) 476 ([M + H]$^+$, 100%), 122 ([CH$_3$OBn]$^+$, 25).

(2*R*,4*S*)-2-Ferrocenyl-3-pivaloyl-4-(3′-indolylmethyl)-1,3-oxazolidin-5-one 35



Following *general procedure 2*, imine **17** (1.78 g, 4.22 mmol) gave **35** as a yellow crystalline solid (1.76 g, 86%, >98% de); $C_{27}H_{28}N_2O_3Fe$ requires C, 66.95; H, 5.8; N, 5.8%; found C, 67.0; H, 5.7; N, 5.6%; mp 145–147 °C; $[\alpha]_D^{22}$ +252 (*c* 0.1 in $CHCl_3$); ν_{max} (KBr) 3400 (N–H), 2972, 2910 (C–H), 1786 (OC=O), 1640 (NC=O), 1169; δ_H (500 MHz, $CDCl_3$) 0.98 (9H, s, C(CH_3)$_3$), 3.47 (1H, dd, *J* 15.0, 2.5, C(4)CH_AH$_B$), 3.71 (1H, dd, *J* 15.0, 5.5, C(4)CH$_A$$H_B$), 4.12–4.32 (4H, m, *Cp*), 4.20 (5H, s, *Cp′*), 4.97 (1H, dd, *J* 5.5, 2.5, C(4)*H*), 6.09 (1H, s, C(2)*H*), 7.06 (1H, d, *J* 2.5, *Ar*), 7.14–7.20 (2H, m, *Ar*), 7.37–7.63 (2H, m, *Ar*), 8.29 (1H, br s, N*H*); δ_C (125.7 MHz, $CDCl_3$) 26.8 (C(4)*C*H$_2$), 28.1 (C(*C*H$_3$)$_3$), 40.7 (*C*(CH$_3$)$_3$), 58.8 (*C*(4)), 65.7, 68.0, 68.5, 70.0 (4 × *Cp*), 69.2 (5 × *Cp′*), 87.3 (1 × *Cp*), 88.4 (*C*(2)), 108.8, 127.7, 135.9 (3 × *Ar*), 111.0, 119.4, 119.7, 122.1, 123.8 (5 × *Ar*), 172.7, 178.8 (*C*(5), N*C*O); *m*/*z* (APCI$^+$) 485 ([M + H]$^+$, 100%), 484 ([M]$^+$, 99).

Acknowledgements

We thank the Ministerio de Educación y Cultura of Spain and the British Council for a Fleming Fellowship (F. A.), the DTI and EPSRC for a LINK studentship (A. S. E.) and Oxford Asymmetry Ltd. for support. We are grateful to Dr Rafael Chinchilla (University of Alicante, Spain) for carrying out the *ab initio* calculations.[15]

References

1 A. J. Jung, *Chemistry and Biochemistry of the Amino Acids*, ed. G. C. Barret, Chapman & Hall, London, 1985, pp. 227-245; D. Schirlin, F. Gerhart, J. M. Horsperger, M. Hamon, J. Wagner and M. J. Jung, *J. Med. Chem.*, 1988, **31**, 30; D. E. Zembower, J. A. Gilbert and M. M. Ames, *J. Med. Chem.*, 1993, **36**, 305.

2 R. M. Williams, *Synthesis of Optically Active* α*-Amino Acids*, eds. J. E. Baldwin, P. D. Magnus, Pergamon Press, Oxford, 1989; C. Cativiela and M. D. Díaz-de-Villegas, *Tetrahedron: Asymmetry*, 1998, **9**, 3517; C. Cativiela and M. D. Díaz-de-Villegas, *Tetrahedron: Asymmetry*, 2000, **11**, 645.

3 For a review, see: D. Seebach, A. R. Sting and M. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2708.

4 For examples see: D. Seebach, B. Lamatsch, R. Mastutz, A. K. Beck, M. Dobler, M. Egli, R. Fitzi, M. Gautschi, B. Herradon, P. C. Hibder, J. I. Irwin, R. Locher, M. Maestro, T. Maetzke, A. Mourino, E. Pfammatter, D. A. Plattner, C. Schickli, W. Bernd Schweizer, P. Seiler and G. Stucky, *Helv. Chim. Acta*, 1992, **75**, 913; M. Gander-Cooper and D. Seebach, *Helv. Chim. Acta*, 1988, **71**, 224; E. Altmann, K. Nebel and M. Mutter, *Helv. Chim. Acta*, 1991, **74**, 800; K. Nebel and M. Mutter, *Tetrahedron*,

1988, **44**, 4793; D. Seebach, E. Juaristi, D. D. Miller, C. Schickli and T. Weber, *Helv. Chim. Acta*, 1987, **70**, 237.
5 For a complementary strategy that allows access to both *cis*- and *trans*-oxazolidinones stereoselectively from *N*-Cbz-(*S*)-Phe, see: M. J. O'Donnell, Z. Fang, X. Ma and J. C. Huffman, *Heterocycles*, 1997, **46**, 617. Also see: W. D. Shrader and C. K. Marlowe, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 2207.
6 D. Seebach and A. Fadel, *Helv. Chim. Acta*, 1985, **68**, 1243.
7 A. Fadel and J. Salaün, *Tetrahedron Lett.*, 1987, **28**, 2243.
8 R. Naef and D. Seebach, *Helv. Chim. Acta*, 1985, **68**, 135.
9 E. Napolitano and V. Farina, *Tetrahedron Lett.*, 2001, **42**, 3231; M. Eriksson, E. Napolitano, J. Xu, S. Kapadia, D. Byrne, L. Nummy, N. Grinberg, S. Shen, H. Lee and V. Farina, *Chimia*, 2006, **60**, 566.
10 (*a*) F. Alonso and S. G. Davies, *Tetrahedron: Asymmetry*, 1995, **6**, 353; (*b*) F. Alonso, S. G. Davies, A. S. Elend and J. L. Haggitt, *J. Chem. Soc., Perkin Trans. 1*, 1998, 257; (*c*) F. Alonso, S. G. Davies and C. A. P. Smethurst, *J. Organomet. Chem.*, 1998, **553**, 463.
11 D. Seebach, R. Imwinkelried, T. Weber, ed. R. Scheffold, *Modern Synthetic Methods*, Springer Verlag, Berlin, 1986, vol. 4, pp. 174-176. For related examples see: T. Weber, R. Aeschimann, T. Maetke and D. Seebeach, *Helv. Chim. Acta*, 1986, **69**, 1365; N. A. Paras and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2002, **124**, 7894.
12 Single point energies were obtained by *ab initio* calculations performed at the B·CYP/6-31G level for *cis*-**7** and *trans*-**11** of –2262.569254 au and –2262.567044 au, respectively.
13 F. Alonso, S. G. Davies, A. S. Elend, M. A. Leech, P. M. Roberts, A. D. Smith and J. E. Thomson, *Org. Biomol. Chem.*, 2008, **6**, DOI: 10.1039/b814453b.
14 See, for instance: M. Rosenblum, A. K. Banerjee, N. Danieli, R. W. Fish and V. Schlatter, *J. Am. Chem. Soc.*, 1963, **85**, 316; U. T. Mueller-Westerhoff, Z. Yang and G. Ingram, *J. Organomet. Chem.*, 1993, **463**, 163.
15 The zero-point energies were obtained at HF/3-21G; see: A. P. Scott and L. Radom, *J. Phys. Chem.*, 1996, **100**, 16502.

