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2-Nitroferrocenyloxazolines: precursors to nitrofulvalenes and derivatives of ($_pS$)- and ($_pR$)-2-aminoferrocenecarboxylic acids

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Abstract

Diastereoselective lithiation of (*S*)-2-ferrocenyl-4-(1-methylethyl)oxazoline, followed by addition of N_2O_4, gave (*S*)-2-[($_pS$)-2-nitroferrocenyl]-4-(1-methylethyl)oxazoline which was subsequently converted into derivatives of ($_pS$)-2-aminoferrocenecarboxylic acid. The corresponding ($_pR$)-derivatives were obtained through use of a removable TMS blocking group. The 2-nitroferrocenyloxazolines produced in this work underwent facile photo-decomplexation to give 2-nitrocyclopentadienyliden-1,3-oxazolidenes.

1. Introduction

Several reports have appeared in recent years on the preparation of chiral amino acid derivatives containing a metallocene or aromatic metal-carbonyl as a component of the alpha-substituent.[1] However, no metal-containing amino acid derivatives are known that utilise the planar chirality of a 2-amino-1-carboxylic acid substitution pattern in a π-bonded organometallic. Such a β-amino acid derived from the ferrocene nucleus is of interest as **1** is structurally analogous to both *cis*-pentacin **2**, an antifungal antibiotic,[2] and the *cis*-substituted norbornene derivative **3**, which has been shown to act as a turn inducer for the formation of parallel and antiparallel β-sheets.[3] In light of recent activity into the synthesis of non-racemic ferrocene derivatives,[4] and in particular the development of highly diastereoselective lithiation of ferrocenyl oxazolines,[5] we report herein the application of this methodology to the synthesis of stable derivatives of **1**,[6] and describe an unprecedented photo-decomplexation of nitroferrocenes into nitrofulvalenes.

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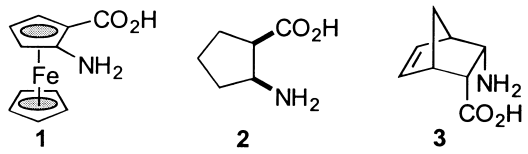
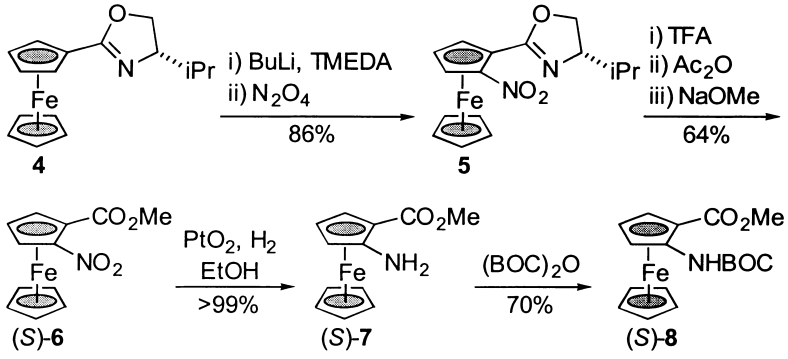


2. Results and discussion

Addition of dinitrogen tetroxide to ferrocenyl lithium is a low yielding though direct route to nitroferrocene, which is in turn readily reduced to aminoferrocene.[7] Encouraged by the recently reported methodology for the high yielding N_2O_4 nitration of aryl lithiums,[8] we found that a slight modification of this procedure with the ferrocenyl lithium derived from **4** gave a high yield of the 2-nitroferrocenyl oxazoline **5**, which was obtained as a single diastereoisomer (Scheme 1).



Scheme 1.

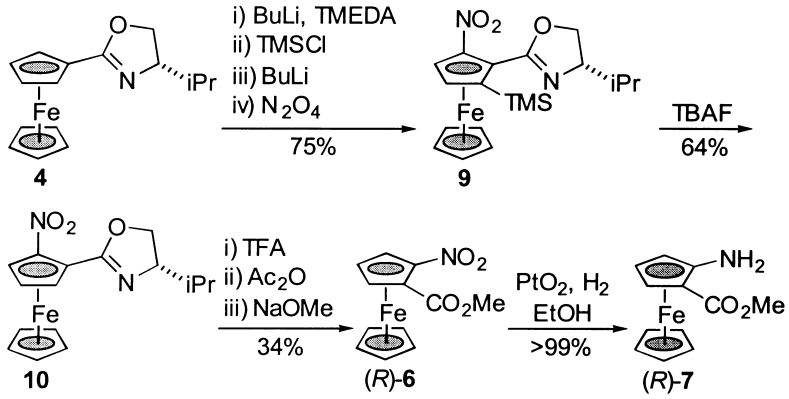
The oxazoline ring of this light-sensitive dark-red material was ring opened,[9] and the resulting 2-acetamido-3-methylbutyl ester was transesterified with sodium methoxide to give the (*S*)-methyl ester **6**. This in turn was cleanly reduced with Adams' catalyst and 1 atmosphere of hydrogen to give (*S*)-methyl 2-aminoferrocenecarboxylate (**7**). When this reduction was performed prior to transesterification, the resulting amino ester underwent rapid decomposition, and all attempts to obtain the parent amino acid **1** by hydrolysis of **7** only resulted in decomposition of the product produced in the reaction mixture. Although **7** was found to be stable to air, moisture and light, partial decomposition occurred on storage of this amorphous dark-brown material for several weeks. This was averted by conversion of **7** to the more stable *N*-Boc methyl ester **8**.

The enantiomers (*R*)-**6** and (*R*)-**7** were also obtained from **4** through use of a removable trimethylsilyl blocking group[5f] which was introduced in a one-pot procedure prior to further lithiation and addition of N_2O_4 (Scheme 2).

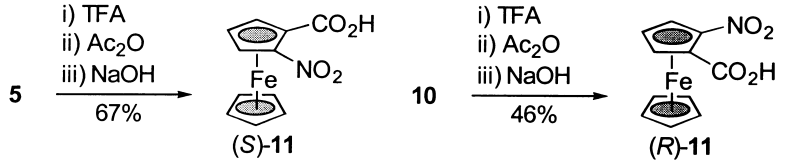
The resulting trisubstituted ferrocene **9**, also obtained as a single diastereoisomer, was desilylated and compound **10** was ring opened and transesterified as before to give (*R*)-**6**, and (*R*)-**7** on reduction.

Nitro-oxazolines **5** and **10** were further ring opened and hydrolysed to give repectively the nitroacids (*S*)-**11** and (*R*)-**11** (Scheme 3). Provided they are stored in the dark these are otherwise air stable, and both enantiomers may be regarded as amine protected derivatives of (*S*)- and (*R*)-**1**. However, attempts to obtain the parent amino acids themselves by hydrogenation of **11** again resulted in decomposition of the products produced in the reaction mixtures.

All of the nitroferrocene derivatives reported in this work were found to be very light sensitive. When a solution of **5** in EtOAc was exposed to indirect sunlight, either under nitrogen or exposed to air, the

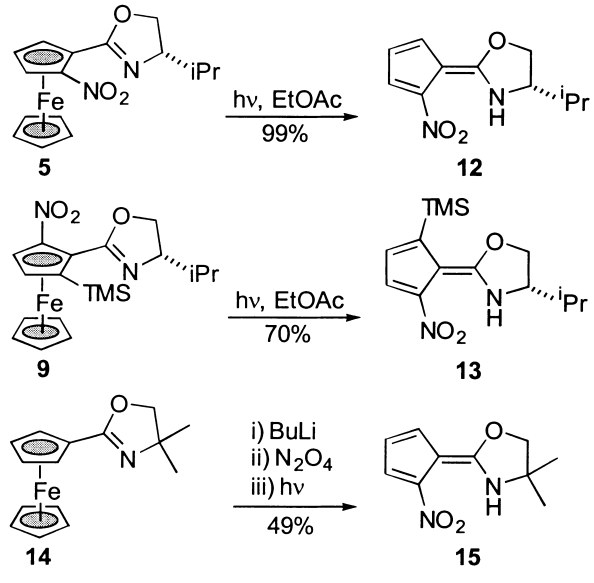


Scheme 2.



Scheme 3.

colour of the solution changed within minutes from dark-red to yellow. Passage through a short plug of silica and evaporation of the solvent gave an essentially quantitative yield of the nitrofulvalene **12** (Scheme 4).



Scheme 4.

Similarly **9** was cleanly degraded into the trimethylsilylnitrofulvalene (**13**), and the use of this chemistry for the one-pot conversion of ferrocenyloxazolines into fulvalenes was demonstrated with the transformation of **14** into **15**. The structure of this latter fulvalene was confirmed with an X-ray crystal structure analysis, revealing that the single isomer obtained is in the *E*-configuration (Fig. 1).[10] The structures assigned to **12** and **13** assume this same geometry, an assumption supported by the formation of **12** from **13** on desilylation. These degradations are not promoted by either acid or base in the absence

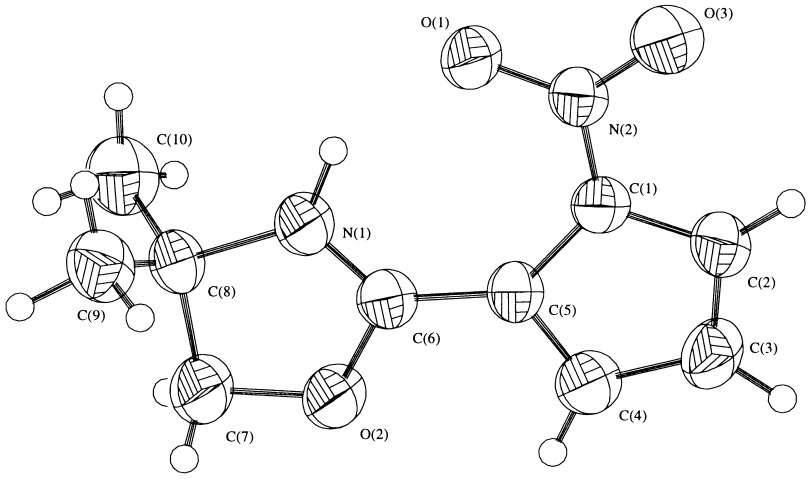


Figure 1. Molecular structure of **15**. Selected bond distances (Å): C(1)–C(2) 1.394(3), C(2)–C(3) 1.385(3), C(3)–C(4) 1.382(3), C(4)–C(5) 1.402(3), C(5)–C(1) 1.432(2), C(5)–C(6) 1.399(3), C(6)–O(2) 1.333(2), C(6)–N(1) 1.306(2)

of light, and are analogous to the standard decomplexation protocol for arene chromium tricarbonyl derivatives. No identifiable products were obtained on light degradation of the non-oxazoline containing nitroferrocenes, and the importance of the oxazoline substituent is clear in permitting the formation of the fulvalene moiety through concomitant reduction of the C=N bond.

In conclusion, we have demonstrated that use of lithiated ferrocenyloxazolines in conjunction with N_2O_4 as an electrophilic quench leads to the diastereoselective synthesis of 2-nitroferrocenyloxazolines. These are readily transformed into derivatives of a β-amino acid displaying planar chirality, and are also found to undergo a novel photo-decomplexation reaction to give nitrofulvalenes. In our ongoing work we are exploring further derivatives of **1** of potential therapeutic interest, and studying the reaction chemistry of these novel fulvalene structures.

3. Experimental

3.1. General

Diethyl ether and tetrahydrofuran were distilled from sodium benzophenone ketyl and TMEDA was distilled from calcium hydride. Petroleum ether refers to that fraction boiling in the range 40–60°C and hexane to the fraction boiling in the range 65.5–70°C. Column chromatography was performed on SiO_2 (40–63 μm). Melting points are uncorrected. NMR spectra were recorded on a Bruker DPX 400 MHz spectrometer or a Bruker WM 360 MHz spectrometer. R_f values were recorded on silica plates in 40% EtOAc/petroleum ether 40–60 unless otherwise stated.

*3.2. Synthesis of (S)-2-[($_p$S)-2-nitroferrocenyl]-4-(1-methylethyl)oxazoline (**5**)*

A dark-orange solution of **4** (1.015 g, 3.42 mmol) and TMEDA (0.67 ml, 4.44 mmol) in dry Et_2O (40 ml) under nitrogen was cooled to −78°C. To this was added dropwise BuLi (2.11 ml, 4.43 mmol), the reaction mixture darkening to red/brown. After stirring at −78°C for 2 h, the Schlenk tube containing the reaction mixture was transferred to an ice bath and the solvent removed in vacuo and replaced with dry THF (40 ml). This solution was transferred via cannula to a 500 ml flask fitted with a sidearm nitrogen

inlet and septum, and immersed in a liquid nitrogen bath with vigorous swirling to ensure that the inner surface of the flask was coated with a thin layer of frozen reactant. At this point the contents of the flask were protected from light by covering with aluminium foil. In a separate pre-weighed Schlenk tube which had been evacuated at −78°C and sealed, brown N_2O_4 gas (CAUTION!) was condensed to a light blue solid (ca. 2 g). The cooling bath was then removed and the contents allowed to warm to room temperature under nitrogen. Excess N_2O_4 gas was bled off with a needle until 0.78 g (8.5 mmol) of brown liquid remained. Rapid transfer of the N_2O_4 via cannula to the frozen organolithium/THF solid was effected, followed by immersion of the reaction vessel in a room temperature methanol bath with vigorous swirling. The reaction was complete in ca. 30 s giving a dark-brown non-homogeneous solution. Excess N_2O_4 and the solvent were removed in vacuo, and finally the flask was placed in a warm water bath to give a dark oily residue. The following work-up was performed in the absence of light. The residue was taken up in CH_2Cl_2 (80 ml), filtered and the residue washed with CH_2Cl_2 (2×20 ml). The combined filtrates were washed with H_2O, dried (Na_2SO_4), filtered and evaporated. The crude product was purified by column chromatography (40% EtOAc/petroleum ether) to give **5** (1.005 g, 86%) as a dark-red oil that crystallised on standing.

Mp 117–119°C; $[\alpha]_D^{19}$ −163 (*c* 0.054, EtOH); ν_{max} (Nujol) 1651 (C=N), 1519 (NO_2) cm^{-1}; δ_H ($CDCl_3$) 0.98 (3H, d, *J* 6.8, –C*H*$_3$), 1.04 (3H, d, *J* 6.8, –C*H*$_3$), 1.86–1.93 (1H, m, –C*H*$(CH_3)_2$), 4.05–4.11 (1H, m, –NC*H*–), 4.18 (1H, t, *J* 8.2, –OC*H*H–), 4.44 (1H, t, *J* 8.2, –OCH*H*–), 4.44 (5H, s, C_5H_5), 4.54 (1H, t, *J* 2.8, Fc), 4.84 (1H, dd, *J* 2.8, 1.7, Fc), 5.30 (1H, dd, *J* 2.8, 1.7, Fc), δ_C {^{1}H} ($CDCl_3$) 18.01 (–*C*H_3), 18.73 (–*C*H_3), 32.43 (–*C*H$(CH_3)_2$), 69.03 (Fc), 69.10 (Fc), 70.48 (–O*C*H_2–), 70.91 (Fc), 72.53 (Fc), 73.09 (–N*C*H–), 73.19 (*C*$_5$H$_5$), 102.10 (Fc), 161.50 (–*C*=N–); *m/z* (EI) 342 (M^+, 68%), 312 (100), 226 (39), 149 (38), 121 (88); R_f 0.42. Found: C, 56.17; H, 5.18; N, 7.99. $C_{16}H_{18}FeN_2O_3$ requires C, 56.16; H, 5.30; N, 8.19%.

3.3. Synthesis of ($_p$S)-methyl 2-nitroferrocenecarboxylate (**6**)

The following procedure was performed in the absence of light. To a dark-red solution of **5** (0.294 g, 0.86 mmol) in THF (10 ml) was added H_2O (0.16 ml), trifluoroacetic acid (0.37 ml) and Na_2SO_4 (1.83 g). This suspension was stirred overnight at room temperature, filtered and evaporated. The resulting black residue was taken up in CH_2Cl_2 (13 ml), followed by addition of pyridine (0.40 ml) and acetic anhydride (0.75 ml). This was stirred overnight at room temperature, washed with HCl (1 M, 3×11 ml) then H_2O (11 ml), dried (Na_2SO_4), filtered and evaporated. The crude product was purified by column chromatography (60% EtOAc/petroleum ether) to give (0.236 g, 68%) of the intermediate nitro ester as a light sensitive dark-red oily solid.

ν_{max} (liquid film) 3394 (N–H), 1726 (C=O ester), 1650 (C=O amide), 1520 (NO_2); δ_H ($CDCl_3$) 0.94 (3H, d, *J* 6.8, –C*H*$_3$), 0.98 (3H, d, *J* 6.8, –C*H*$_3$), 1.76–1.85 (1H, m, –C*H*$(CH_3)_2$), 2.03 (3H, s, –COC*H*$_3$), 3.97–4.01 (1H, m, –NHC*H*–), 4.21 (1H, dd, *J* 11.4, 3.4, –OC*H*H–), 4.37 (5H, s, C_5H_5), 4.38 (1H, dd, *J* 11.4, 4.4, –OCH*H*–), 4.56 (1H, t, *J* 2.8, Fc), 4.93 (1H, dd, *J* 2.6, 1.7, Fc), 5.28 (1H, dd, *J* 2.5, 1.7, Fc), 5.93 (1H, brd, *J* 9.2, –N*H*–); δ_C {^{1}H} ($CDCl_3$) 19.72 (–*C*H_3), 19.84 (–*C*H_3), 23.75 (–*C*H$(CH_3)_2$), 53.74 (–*C*HNH–), 66.14 (–O*C*H_2–), 70.18 (Fc), 71.88 (Fc), 75.53 (Fc), 73.99 (*C*$_5$H$_5$), 74.21 (Fc), 126.28 (Fc), 168.48 (*C*=O), 170.52 (*C*=O); *m/z* (EI) 402 (M^+, 9%), 128 (30), 43 (100).

To a red solution of the nitro ester (0.236 g, 0.59 mmol) in THF (5 ml) and MeOH (5 ml) was added sodium methoxide (0.32 g, 5.9 mmol) in MeOH (10 ml). After stirring at room temperature overnight the mixture was neutralised with acetic acid and the solvent removed without heating in vacuo. The residue was taken up in CH_2Cl_2 (15 ml) and washed with H_2O (15 ml), dried (Na_2SO_4), filtered and

evaporated. The crude product was purified by column chromatography (30% EtOAc/petroleum ether) to give **6** (0.160 g, 94%, 64% from **5**) as a dark-red oil.

$[\alpha]_D^{21}$ +170 (*c* 0.03, $CHCl_3$); ν_{max} (liquid film) 1727 (C=O), 1519 (NO_2), 1329 (NO_2) cm^{-1}; δ_H ($CDCl_3$) 3.90 (3H, s, –C*H*$_3$), 4.44 (5H, s, C_5H_5), 4.57 (1H, t, *J* 2.8, Fc), 4.94 (1H, dd, *J* 2.8, 1.5, Fc), 5.24 (1H, dd, *J* 2.8, 1.5, Fc); δ_C {^{1}H} ($CDCl_3$) 52.55 (–*C*H$_3$), 69.18 (Fc), 69.98 (Fc), 71.87 (Fc), 72.96 (Fc), 73.51 (*C*$_5$H$_5$), 104.8 (Fc), 168.02 (*C*=O); *m/z* (EI) 289 (M^+, 100%), 259 (62), 150 (28), 121 (63), 81 (81), 56 (78). Found C, 50.01; H, 3.93; N, 4.99. $C_{12}H_{11}FeNO_4$ requires C, 49.86; H, 3.84; N, 4.85.

3.4. Synthesis of ($_p$S)-methyl 2-aminoferrocenecarboxylate (7)

A solution of **6** (0.090 g, 0.31 mmol) in EtOH (10 ml) containing PtO_2 (0.009 g) was stirred under hydrogen at atmospheric pressure and room temperature for 2 h. The resultant mixture was filtered through Celite and the solvent removed in vacuo to give **7** (0.080 g, >99%) as a light-orange oil.

$[\alpha]_D^{19}$ −212 (*c* 0.165, EtOH); ν_{max} (liquid film) 3442 and 3359 (NH_2), 1699 (C=O) cm^{-1}; δ_H ($CDCl_3$) 1.70 (2H, brs, –N*H*$_2$), 3.85 (3H, s, C*H*$_3$), 4.06 (1H, t, *J* 2.6, Fc), 4.10 (5H, s, C_5H_5), 4.23 (1H, dd, *J* 2.6, 1.5, Fc), 4.46 (1H, dd, *J* 2.6, 1.5, Fc), δ_C {^{1}H} ($CDCl_3$) 51.27 (–*C*H$_3$) 57.54 (Fc), 59.15 (Fc), 64.19 (Fc), 65.01 (Fc), 70.20 (–*C*$_5$H$_5$), 110.35 (Fc), 174.07 (–*C*O$_2$–), *m/z* (EI) 259 (M^+, 4%), 121 (81), 106 (38), 69 (100); R_f 0.60. Found 259.0302, $C_{12}H_{13}FeNO_2$ requires 259.0296.

3.5. Synthesis of ($_p$S)-methyl 2-N-tert-butoxycarbonylaminoferrocenecarboxylate (8)

A yellow solution of **7** (0.034 g, 0.13 mmol), BOC_2O (0.034 g, 0.16 mmol) and DMAP (0.017 g, 0.14 mmol) in CH_2Cl_2 (10 ml) was stirred under nitrogen at room temperature overnight. Removal of the solvent in vacuo was followed by column chromatography (5% EtOAc/petroleum ether) to give **8** (0.033 g, 70%) as a yellow solid.

$[\alpha]_D^{22}$ −228 (*c* 0.28, $CHCl_3$); ν_{max} (liquid film) 3370 (NH), 1724 (C=O), 1688 (C=O) cm^{-1}; δ_H ($CDCl_3$) 1.45 (9H, s, –OC(C*H*$_3$)$_3$), 3.79 (3H, s, –OC*H*$_3$), 4.09 (5H, s, C_5H_5), 4.14 (1H, t, *J* 2.7, Fc), 4.44 (1H, dd, *J* 2.5, 1.5, Fc), 5.29 (1H, brs, Fc), 7.67 (1H, brs, –N*H*–); δ_C {^{1}H} ($CDCl_3$) 27.29 (–C(*C*H$_3$)$_3$), 50.66 (–O*C*H$_3$), 61.72 (Fc), 63.77 (Fc), 65.64 (Fc), 69.53 (*C*$_5$H$_5$), 98.80 (Fc), 124.86 (Fc), 152.21 (–*C*O$_2$^{t}Bu), 173.90 (–*C*O$_2$Me), not observed (–*C*(CH$_3$)$_3$); *m/z* (EI) 359 (M^+, 11%), 258 (3), 121 (8), 56 (100). Found 359.0812, $C_{17}H_{21}FeNO_4$ requires 359.0819.

3.6. Synthesis of (S)-2-[($_p$S)-2-nitro-5-(trimethylsilyl)ferrocenyl]-4-(1-methylethyl)oxazoline (9)

A solution of **4** (1.170 g, 3.94 mmol) in Et_2O (40 ml) was lithiated with BuLi (2.31 ml, 5.1 mmol) in the presence of TMEDA (0.77 ml, 5.1 mmol) as described for the synthesis of **5**. After stirring at −78°C for 2 h, the mixture was warmed to 0°C for 15 min prior to the addition of TMSCl (0.65 ml, 5.1 mmol) and stirring at room temperature for a further 15 min. Additional Et_2O (10 ml) and TMEDA (0.62 ml, 4.12 mmol) were added, the reaction mixture cooled to −78°C, and BuLi (1.86 ml, 4.12 mmol) added dropwise. After stirring at −78°C for 2 h, followed by 15 min at 0°C, the solvent was removed in vacuo (without heating above room temperature) and replaced by THF (40 ml). The resulting dark-red solution was frozen and treated with N_2O_4 (0.38 g, 4.1 mmol — CAUTION!) as described for the synthesis of **5**. As before the reaction was complete in ca. 30 s when the flask containing the frozen reactants was vigorously shaken in a room temperature methanol bath to give a dark-red solution. Excess N_2O_4 was removed under high vacuum. Water (100 ml) was added to the THF solution and the product extracted with CH_2Cl_2 (3×50 ml). The organic extracts were combined and washed with H_2O (50 ml),

dried (Na_2SO_4), filtered, and the solvent removed in vacuo. Purification by column chromatography (10% EtOAc/petroleum ether) in the absence of light gave **9** (1.22 g, 75%) as a dark-red oil that crystallised on standing.

Mp 78–80°C; $[\alpha]_D^{19}$ +24 (*c* 0.44, $CHCl_3$); ν_{max} (liquid film) 1652 (C=N), 1519 (NO_2) cm^{-1}; δ_H ($CDCl_3$) 0.22 (9H, s, –Si(C*H*$_3$)$_3$), 0.91 (3H, d, *J* 6.7, –C*H*$_3$), 1.05 (3H, d, *J* 6.7, –C*H*$_3$), 1.74–1.78 (1H, m, –C*H*(CH$_3$)$_2$), 3.87–3.95 (1H, m, –NC*H*–), 4.06 (1H, dd, *J* 9.8, 8.3, –OC*H*H–), 4.35 (1H, d, *J* 2.7, Fc), 4.36 (5H, s, C_5H_5), 4.45 (1H, dd, *J* 9.8, 8.3, –OCH*H*–), 5.30 (1H, d, *J* 2.7, Fc), δ_C {^{1}H} ($CDCl_3$) −0.34 (Si(*C*H$_3$)$_3$), 19.14 (–*C*H$_3$), 19.67 (–*C*H$_3$), 33.20 (–*C*H(CH$_3$)$_2$), 69.49 (Fc), 69.57 (Fc), 71.64 (–O*C*H$_2$–), 73.27 (*C*$_5$H$_5$), 74.29 (–N*C*H– and Fc), 103.35 (Fc), 161.65 (*C*=N); *m/z* (EI) 414 (M^+, 43%), 384 (56), 369 (100), 354 (66), 268 (54), 149 (54), 121 (82), 73 (95); R_f 0.97. Found: C, 55.07; H, 6.45; N, 6.52. $C_{19}H_{26}FeN_2O_3Si$ requires C, 55.07; H, 6.32; N, 6.76.

3.7. Synthesis of (S)-2-[($_p$*R)-2-nitroferrocenyl]-4-(1-methylethyl)oxazoline (**10**)*

A dark-red solution of **9** (0.563 g, 1.36 mmol) and 1M TBAF in THF (55 ml) containing approximately 5% H_2O was heated at reflux under nitrogen for 8 h in the dark. The resultant dark-red solution was evaporated in vacuo to low volume and partitioned between Et_2O (15 ml) and H_2O (15 ml). After separation, the aqueous phase was further extracted with Et_2O (15 ml) and the organics combined, dried ($MgSO_4$), filtered and the solvent removed in vacuo. Purification by column chromatography (40% EtOAc/petroleum ether) gave **10** (0.30 g, 64%) as a dark-red oil.

$[\alpha]_D^{19}$ −211 (*c* 0.065, EtOH); ν_{max} (liquid film) 1651 (C=N), 1519 (NO_2) cm^{-1}; δ_H ($CDCl_3$) 1.00 (1H, d, *J* 6.8, –C*H*$_3$); 1.05 (1H, d, *J* 6.8, –C*H*$_3$), 1.88–1.95 (1H, m, –C*H*(CH$_3$)$_2$), 4.13–4.06 (1H, m, –NC*H*–), 4.21 (1H, dd, *J* 9.6, 8.3, –OC*H*H–), 4.42 (1H, dd, *J* 9.6, 8.3, –OCH*H*–), 4.43 (5H, s, C_5H_5) 4.54 (1H, t, *J* 2.8, Fc), 4.89 (1H, dd, *J* 2.8, 1.7, Fc), 5.30 (1H, dd, *J* 2.8, 1.7, Fc), δ_C {^{1}H} ($CDCl_3$) 17.95 (–*C*H$_3$), 18.57 (–*C*H$_3$), 32.35 (–*C*H(CH$_3$)$_2$), 69.06 (Fc), 69.12 (Fc), 70.53 (–O*C*H$_2$–), 71.02 (Fc), 72.85 (Fc), 73.34 (*C*$_5$H$_5$), 101.83 (Fc), 161.97 (*C*=N); *m/z* (EI) 342 (M^+, 78%), 312 (100), 226 (35), 210 (29), 121 (85), 81 (47); R_f 0.42. Found: C, 56.11; H, 5.17; N, 8.58. $C_{16}H_{18}FeN_2O_3$ requires C, 56.16; H, 5.30; N, 8.18.

3.8. Synthesis of ($_p$*R)-methyl 2-nitroferrocenecarboxylate (**6**) and (*$_p$*R)-methyl 2-aminoferrocene-carboxylate (**7**)*

A solution of **10** (0.280 g, 0.082 mmol) in THF (6 ml) was ring opened as previously described for the synthesis of ($_pS$)-**6**. Column chromatography (60% EtOAc/petroleum ether) gave 0.177 g (54%) of the intermediate nitro ester as a dark-red oil, δ_H ($CDCl_3$) 0.96 (3H, d, *J* 6.8, –C*H*$_3$), 0.97 (3H, d, *J* 6.8, –C*H*$_3$), 1.76–1.86 (1H, m, –C*H*(CH$_3$)$_2$), 2.10 (3H, s, –COC*H*$_3$), 4.03–4.10 (1H, m, –OCH$_2$C*H*–), 4.39 (2H, dd, *J* 5.8, 4.5, –OC*H*$_2$–), 4.45 (5H, s, C_5H_5), 4.62 (1H, t, *J* 2.8, Fc), 5.03 (1H, dd, *J*, 2.8, 1.9, Fc), 5.32 (1H, dd, *J* 2.8, 1.9, Fc), 5.92 (1H, brd, *J* ca. 10, –N*H*–). Transesterification as previously described gave ($_pR$)-**6** (0.081 g, 34% from **10**). Hydrogenation, as previously described for ($_pS$)-**7**, gave ($_pR$)-**7** (0.072 g, >99%).

3.9. Synthesis of ($_p$*S)- and (*$_p$*R)-2-nitroferrocenecarboxylic acid (**11**)*

To a solution of the intermediate nitro ester (0.201 g, 0.50 mmol), generated as described in the synthesis of ($_pS$)-**6**, in THF (5 ml) and MeOH (5 ml), was added a solution of NaOH (0.100 g, 2.50 mmol) in MeOH (5 ml) and H_2O (5 ml). The resulting mixture was stirred in the absence of light at

room temperature overnight. This was then neutralised with acetic acid and partitioned between H_2O (10 ml) and CH_2Cl_2 (10 ml). The aqueous phase was further extracted with CH_2Cl_2 (10 ml), and the organics combined, dried (Na_2SO_4), filtered and evaporated. The crude products were purified by column chromatography (100% EtOAc) to give ($_pS$)-**11** (0.137 g, >99%, 67% from **5**). Ring opening as previously described for ($_pR$)-**6** and hydrolysis as described for ($_pS$)-**11** gave ($_pR$)-**11** (0.022 g, 46% from **10**).

Mp 123–125°C; $[\alpha]_D^{19}$ +625 (*c* 0.004, $CHCl_3$ for ($_pS$)-**11**); ν_{max} (Nujol) 3300 (OH), 1716 (C=O), 1516 (NO_2), 1329 (NO_2) cm^{-1}; δ_H ($CDCl_3$) 4.46 (5H, s, C_5H_5), 4.87 (1H, t, *J* 2.9, Fc), 5.45 (1H, dd, *J* 2.9, 2.0, Fc), 5.52 (1H, dd, *J* 2.9, 2.0, Fc); δ_C {^{1}H} ($CDCl_3$) 68.10 (Fc), 71.85 (Fc), 71.89 (Fc), 73.47 (C_5H_5), 77.22 (Fc), 124.80 (Fc), 166.32 (*C*=O); *m/z* (ES) 276 (MH^++1, 100%), 258 (22); R_f 0.68 (30% MeOH/EtOAc). Found: C, 48.15; H, 3.54; N, 4.93. $C_{11}H_9FeNO_4$ requires C, 48.04; H, 3.30; N, 5.09.

*3.10. Synthesis of (*S*)-(*E*)-2-(2-nitrocyclopentadienyliden)-4-(1-methylethyl)-1,3-oxazolidene (**12**)*

A red solution of **5** (0.010 g, 0.029 mmol) in EtOAc (10 ml) was exposed to indirect sunlight for 4 h, leaving a bright-yellow solution. Removal of the solvent in vacuo was followed by column chromatography (40% EtOAc/petroleum ether) to give **12** as a bright-yellow powder (0.0064 g, 99%).

Mp 147.5–149°C; $[\alpha]_D^{21}$ +110 (*c* 0.074, $CHCl_3$); ν_{max} (liquid film) 3434 (NH) 1637 (C=C), 1340 (NO_2) cm^{-1}; δ_H ($CDCl_3$) 0.95 (3H, d, *J* 6.7, –C*H*$_3$), 1.00 (3H, d, *J* 6.7, –C*H*$_3$), 1.84–1.92 (1H, m, –C*H*(CH_3)$_2$), 4.03–4.10 (1H, m, –NHC*H*–), 4.47 (1H, dd, *J* 9.1, 6.5, –OC*H*H–), 4.76 (1H, t, *J* 9.2, –OCH*H*–), 6.10 (1H, t, *J* 4.1, –(NO_2)C=CH–C*H*–), 6.98 (1H, dd, *J* 4.1, 2.4, –(NO_2)C–C–C*H*–), 7.34 (1H, dd, *J* 4.1, 2.4, –(NO_2)C=C*H*–), 11.24 (1H, brs, –N*H*–); δ_C {^{1}H} ($CDCl_3$) 17.94 (–*C*H_3), 17.96 (–*C*H_3), 32.31 (–*C*H(CH_3)$_2$), 62.62 (–NH*C*H–), 72.88 (–O*C*H_2–), 77.16 (–NH*C*=C–), 96.75 (–NHC=*C*–), 116.59 (–(NO_2)C=CH–*C*H–), 124.80 (–*C*–NO_2), 126.84 (–(NO_2)C=*C*H–), 128.01 (–(NO_2)C–C–*C*H–); *m/z* (EI) 222 (M^+, 51%), 206 (6), 192 (21), 179 (15), 162 (11), 41 (100). Found 222.1005, $C_{11}H_{14}N_2O_3$ requires 222.1004.

*3.11. Synthesis of (*S*)-(*Z*)-2-(2-nitro-5-trimethylsilylcyclopentadienyliden)-4-(1-methylethyl)-1,3-oxazolidene (**13**)*

Photo-decomplexation of **9** (0.010 g, 0.024 mmol) as described for **12**, followed by removal of the solvent in vacuo and column chromatography (40% EtOAc/petroleum ether) gave **13** (0.005 g, 70%) as a bright-yellow amorphous solid.

$[\alpha]_D^{21}$ +30 (*c* 0.09, $CHCl_3$); ν_{max} (Nujol mull) 3427 (NH), 1652 (C=C) cm^{-1}; δ_H ($CDCl_3$) 0.16 (9H, s, –Si(C*H*$_3$)$_3$), 0.96 (3H, d, *J* 6.7, –C*H*$_3$), 1.01 (3H, d, *J* 6.7, –C*H*$_3$), 1.85–1.92 (1H, m, –C*H*(CH_3)$_2$), 4.06–4.11 (1H, m, –NHC*H*–), 4.48 (1H, dd, *J* 2.5, 6.5, –OC*H*H–), 4.74 (1H, dd, *J* 3.7, 9.0, –OCH*H*–), 6.32 (1H, d, *J* 3.99, –(TMS)C=C*H*–), 7.39 (1H, d, *J* 3.91, –(NO_2)C=C*H*–), 11.55 (1H, brs, –N*H*–); δ_C {^{1}H} ($CDCl_3$) 0.97 (Si(*C*H_3)$_3$), 17.84 (–*C*H_3), 17.91 (–*C*H_3), 32.35 (–*C*H(CH_3)$_2$), 60.36 (–NH*C*H–), 72.41 (–O*C*H_2–), 100.54 ((NO_2)C–*C*), 125.54 ((TMS)C=*C*H–), 126.59 ((NO_2)C=*C*H–), 138.63 (–O*C*=C–), 142.59 (*C*–TMS), 165.47 (*C*–NO_2); *m/z* (EI) 294 (M^+, 10%), 222 (24), 121 (15), 73 (61), 56 (100). Found: C, 57.16; H, 7.44; N, 9.14. $C_{14}H_{22}N_2O_3Si$ requires C, 57.11; H, 7.53; N, 9.51.

*3.12. Synthesis of (*E*)-2-(2-nitrocyclopentadienyliden)-4,4-dimethyl-1,3-oxazolidene (**15**)*

A solution of **14**[11] (0.192 g, 0.68 mmol) in THF (12 ml) was lithiated and nitrated as described for **5**. The solvent and excess N_2O_4 were removed in vacuo and the residue taken up in EtOAc (10 ml). This solution was stirred under laboratory lighting for 5 h, the colour changing from deep-red to bright-

yellow. The solvent was removed in vacuo and the crude product purified by column chromatography (40% EtOAc/petroleum ether) to give bright-yellow crystals of **15** (0.069 g, 49%).

Mp 138–139°C; ν_{max} (Nujol mull) 3191 (NH), 1620 (C=C) cm^{-1}; δ_H ($CDCl_3$) 1.58 (6H, s, (CH_3)$_2$), 4.49 (2H, s, –OCH_2–), 6.17 (1H, t, *J* 4.0, –(NO_2)C=CH–C*H*–), 7.05 (1H, dd, *J* 2.4, 4.1, –(NO_2)C–C–C*H*–), 7.39 (1H, dd, *J* 2.4, 4.0, –(NO_2)C=C*H*–), 11.00 (1H, brs, –N*H*–); δ_C {^{1}H} ($CDCl_3$) 27.08 (–(CH_3)$_2$), 60.65 (–*C*(CH_3)$_2$), 80.94 (–OCH_2–), 97.00 (–(NO_2)C–*C*=C–), 116.49 (–(NO_2)C=CH–*C*H–), 126.63 (–(NO_2)C=*C*H–), 127.88 (–NO_2)C–C–*C*H–), 134.74 (–(NO_2)C–C=*C*–), 164.64 (–(NO_2)*C*–); *m/z* (EI) 208 (M^+, 45%), 178 (20), 106 (60), 63 (100), 56 (50). Found: C, 57.94; H, 5.78; N, 13.28. $C_{10}H_{12}N_2O_3$ requires C, 57.69; H, 5.81; N, 13.45.

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References

1. For a recent review of organometallic-containing α-amino acid derivatives see: Severin, K.; Bergs, R.; Beck, W. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 1635.
2. (a) Konishi, M.; Nishio, M.; Saitoh, K.; Miyaki, T.; Oki, T.; Kawaguchi, H. *J. Antibiotics* **1989**, *42*, 1749. (b) Oki, T.; Hirano, M.; Tomatsu, K.; Numata, K.; Kamei, H. *J. Antibiotics* **1989**, *42*, 1756. (c) Iwamoto, T.; Tsujii, E.; Ezaki, M.; Fujie, A.; Hashimoto, S.; Okuhara, M.; Kohsaka, M.; Imanaka, H.; Kawabata, K.; Inamoto, Y.; Sakane, K. *J. Antibiotics* **1990**, *43*, 1. (d) Kawabata, K.; Inamoto, Y.; Sakane, K.; Iwamoto, T.; Hashimoto, S. *J. Antibiotics* **1990**, *43*, 513. (e) Ohki, H.; Inamoto, Y.; Kawabata, K.; Kamimura, T.; Sakane, K. *J. Antibiotics* **1991**, *44*, 546.
3. Hibbs, D. E.; Hursthouse, M. B.; Jones, I. G.; Jones, W.; Abdul Malik, K. M.; North, M. *J. Org. Chem*. **1998**, *63*, 1496.
4. Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377.
5. (a) Richards, C. J.; Damalidis, T.; Hibbs, D. E.; Hursthouse, M. B. *Synlett* **1995**, 74. (b) Sammakia, T.; Latham, H. A.; Schaad, D. R. *J. Org. Chem*. **1995**, *60*, 10. (c) Nishibayashi, Y.; Uemura, S. *Synlett* **1995**, 79. (d) Sammakia, T.; Latham, H. A. *J. Org. Chem*. **1995**, *60*, 6002. (e) Sammakia, T.; Latham, H. A. *J. Org. Chem*. **1996**, *61*, 1629. (f) Richards, C. J.; Mulvaney, A. W. *Tetrahedron: Asymmetry* **1996**, *7*, 1419. (g) Ahn, K. H.; Cho, C.-W.; Baek, H.-H.; Park, J.; Lee, S. *J. Org. Chem*. **1996**, *61*, 4937.
6. During the course of this work a report appeared on the asymmetric synthesis of 2-aminoferrocenecarboxaldehyde: Riant, O.; Samuel, O.; Flessner, T.; Taudien, S.; Kagan, H. B. *J. Org. Chem*. **1997**, *62*, 6733.
7. Helling, J. F.; Shechter, H. *Chem. Ind*. **1959**, 1157.
8. Tani, K.; Lukin, K.; Eaton, P. E. *J. Am. Chem. Soc*. **1997**, *119*, 1476.
9. Nelson, T. D.; Meyers, A. I. *J. Org. Chem*. **1994**, *59*, 2655.
10. $C_{10}H_{12}N_2O_3$, *M*=208.22, monoclinic; *P*21/*n*, *a*=10.2240(10), *b*=10.2590(10), *c*=4020(10) Å, β=109.219(4), *Z*=4, Mo-K$_\alpha$ radiation λ=0.71069 Å, 3994 reflections were measured giving 1505 unique data. Final *wR*2 and *R* were 0.0950 and 0.0539 for all data [0.0916 and 0.0425 for 1505 with $I>2\sigma(I)$].
11. Schmitt, G.; Klein, P.; Ebertz, W. *J. Organomet. Chem*. **1982**, *234*, 63.