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Synthesis and reactivity of a range of 2-ferrocenyl-3-pivaloyl-1,3-oxazolidin-5-ones

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Abstract

A range of novel 2-ferrocenyl-3-pivaloyl-1,3-oxazolidin-5-ones has been synthesised, both with and without 2-substitution on the ferrocenyl moiety in an effort to develop an asymmetric glycine equivalent. While C-4 alkylation of the parent complex 2-ferrocenyl-3-pivaloyl-1,3-oxazolidin-5-one was successful, the presence of a 2-substituent on the ferrocene ring has been found to prevent C-4 enolisation and hence alkylation. © 1998 Elsevier Science S.A.

Keywords: Oxazolidinone; Ferrocenecarboxaldehyde; Planar chirality

1. Introduction

The ever-growing demand for enantiomerically pure non-proteinogenic α-amino acids continues to stimulate the search for new synthetic methodology in this area [1]. A particularly attractive approach to the synthesis of α-amino acids is via the alkylation reactions of chiral glycine enolate equivalents. Chiral glycine equivalents described to date include Schöllkopf's bislactim ethers [2–4], Seebach's imidazolidinones and oxazolidinones [5], Williams' diphenyloxazinones [6,7] and Myers' ephedrine amides [8].

Based on Seebach's self-replication of chirality strategy, [9,10], we recently described a series of enantiospecific alkylations of alanine (Scheme 1) [11]. The reaction of ferrocene carboxaldehyde **1** with sodium (*S*)-alaninate generated the *E*-imine **2** which cyclised on addition of pivaloyl chloride to give the oxazolidinone **3** as a single *cis*-diastereoisomer. The original alaninate stereogenic centre, C-4 in product **3**, completely controlling the formation of the new C-2 stereogenic centre. Subsequent formation of the enolate **4** from **3** destroys the original C-4 stereogenic centre but this is regenerated completely stereoselectively with retention of configuration during formation of **5**, on addition of an appropriate alkyl bromide, alkylation occurring onto the enolate face distal from the ferrocenyl moiety. Hydrolysis of **5** then releases the α-methyl-α-amino acid **6**.

o-Substituted benzaldehyde chromium tricarbonyl complexes are chiral and nucleophilic additions to the prochiral aldehyde moiety and derived imines have been found to be completely stereoselective [12]. We reasoned therefore that chiral 2-substituted ferrocene carboxaldehydes **7** and derived imines would also undergo stereoselective additions and hence a 2-substituted ferrocenyl group would be expected to impart high stereoselectivity on the formation of the C-2 stereogenic centre of the 3-pivaloyl-1,3-oxazolidin-5-one **8** derived from reaction with glycine and pivaloyl chloride (Scheme 2). Deprotonation of **8** should generate the chiral glycine enolate equivalent which would be expected to alkylate *anti* to the ferrocenyl group, subsequent hydrolysis releasing the corresponding α-amino acid.

We describe herein our efforts to implement the above strategy.

2. Results and discussion

To initiate our studies the parent compound **9** was synthesised from ferrocene carboxaldehyde and sodium glycinate in order to establish enolisation and alkylation conditions. Formation of the imine from ferrocenecar-

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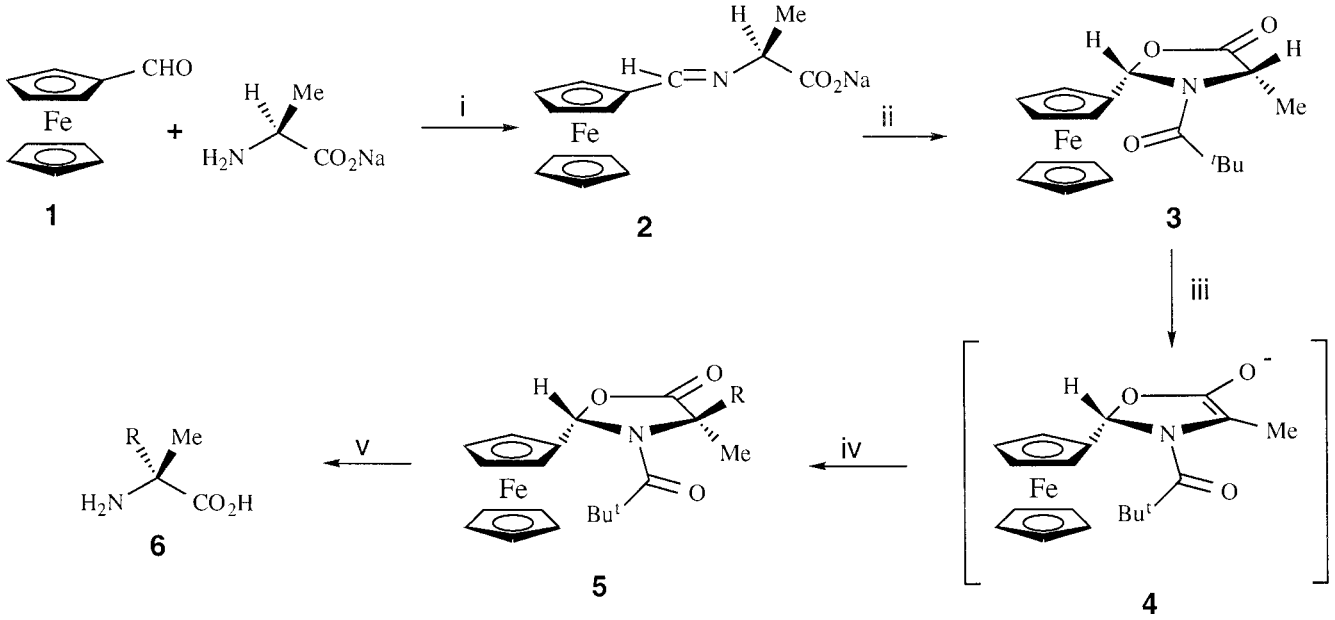


Scheme 1. Reagents and conditions: i, absolute EtOH, 4 Å molecular sieves, r.t.; ii, pivaloyl chloride, CH_2Cl_2, 4 Å molecular sieves, −18°C to r.t. overnight; iii, LDA, THF, −78°C; iv, RX, −78°C to r.t. overnight; v, Amberlyst-15, acetone–H_2O 9:1 overnight.

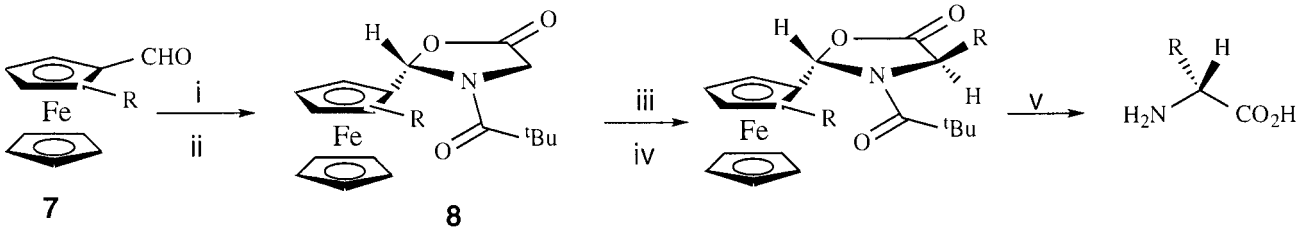
boxaldehyde **1** and sodium glycinate and its subsequent cyclisation with pivaloyl chloride, provided **9** in 77% overall yield (Scheme 3).

Extensive efforts were made to alkylate the glycine derived oxazolidinone **9**. These included the use of different bases such as LDA and NaH, and also the presence of additives such as DMPU [13], LiCl [14] and $(^{i}PrO)_3TiCl$ [15,16]. However, all attempts to methylate or allylate the auxiliary led to the generation of ferrocenecarboxaldehyde, which is presumably formed via ketene generation from the derived enolate or from attack of the base onto one of the carbonyl groups. It did prove possible however to allylate **9** by generation of the enolate with KHMDS pre-treated with 18-crown-6 and subsequent addition of allyl bromide. Thus, treatment of a mixture of **9** and allyl bromide with excess KHMDS/18-crown-6 gave the bisallylated compound **10** in 61% isolated yield (Scheme 4).

A protocol for the allylation of **9** employing one equivalent, relative to oxazolidinone, of the cation free base system KHMDS/18-crown-6 resulted in the formation of the two monoallylated diastereoisomers **11** and **12** in the ratio 55:45 (50%, Scheme 5) together with starting material **9** (39%) and bisallylated compound **10** (11%). It did not prove possible to purify **11** or **12** since all four compounds were unstable to chromatography. Authentic samples of the monoallylated compounds **11** and **12** were prepared, however, from the sodium salt of racemic 2-amino-4-pentenoic acid and ferrocene carboxaldehyde **1**. The diastereoselectivity of the oxazolidinone formation as determined by ^{1}H NMR spectroscopy of the crude reaction product was a 40:60 mixture of **11** and **12** (Scheme 5). Crystallisation from diethyl ether afforded the minor diastereomer **11** (96% d.e.) whilst the major diastereomer **12** was isolated as an oil from the mother liquors with a d.e. of 85%. By comparison of the ^{1}H NMR spectra [1] of these compounds with that for compound **3**, whose structure is known from X-ray analysis, and the fact that the *cis*-compound **12** is expected to be the major diastereoisomer formed in the latter reaction from the sodium salt of racemic 2-amino-4-pentenoic acid and ferrocene carboxaldehyde **1**, assignment of the diastereomer **11** as the *trans* compound and **12** as the *cis* diastereoisomer is possible. Attempts to perform nOe analyses on compounds **11** and **12** were frustrated by their instability with respect to epimerisation at C2 on the timescale of the experiment.

With an alkylation protocol in hand, our attention turned to the development of an asymmetric version of the reaction. The protocol developed by Kagan et al. [18] was employed to produce racemic and enantiomerically enriched [96% e.e.; $[\alpha]_D = -276$ ($c = 0.23$, EtOH)]2-trimethylsilylferrocene carboxaldehyde **13**. In each case, treatment of the aldehyde with sodium glycinate followed by pivaloyl chloride generated the diastereomeric oxazolidinones **14** and **15** in the ratio 2:1 (Scheme 6). Recrystallisation afforded the major diastereoisomer in each case (in 90 and 96% d.e., respectively). The structure of the major diastereoisomer was

[1] Oxazolidinones with a *syn* disposition of ferrocene and oxazolidinone C-4 substituent were found generally to have a chemical shift of the NCHO proton approximately 0.5 ppm higher than the analagous *anti* compounds [17].



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Scheme 2. Reagents and conditions: i, $H_2NCH_2CO_2Na$, absolute EtOH, 4 Å molecular sieves, r.t.; ii, pivaloyl chloride, CH_2Cl_2, 4 Å molecular sieves, −18°C to r.t. overnight; iii, Base, THF, −78°C; iv, RX, −78°C to r.t. overnight; v, Amberlyst-15, acetone–H_2O 9:1 overnight.

tentatively assigned by analogy with the related chromium cases [12].

All attempts to alkylate **14** or a mixture of **14** and **15** failed, even under the conditions previously shown to allylate the parent oxazolidinone **9**. In each case, only 2-trimethylsilylferrocene carboxaldehyde was isolated.

Preparation of the oxazolidinone derived from (−)-(2*R*)-orthotrimethylsilyl ferrocenecarboxaldehyde and sodium (*R*)-D-alaninate afforded a 29:1 mixture of the *cis* and *trans* diastereoisomers **16** and **17** (Scheme 7). Using sodium (*S*)-L-alaninate in an analogous procedure afforded a 1:6 mixture of the corresponding *cis*- and *trans*-diastereomers **18** and **19**. These results indicate that the ferrocenyl group has a directing effect which if fully expressed would give rise to a d.r. of 17.5:1 while the alanine residue of producing a d.r. of 11.5:1 in this reaction, both in favour of the thermodynamically more stable *cis*-diastereomer. The large directing effect calculated for the ferrocenyl unit does not agree with the poor selectivity which was obtained in formation of the glycine derived oxazolidinone (**14** and **15**). It, therefore, seems likely that this is a case where simple application of Masamune's rules [19] do not apply, presumably due to interaction of the two directing centres.

Despite the ferrocenyl derivative **9** undergoing smooth deprotonation and allylation the complexes **16**–**19** proved inert to allylation. In all cases decomposition was observed to regenerate the 2-trimethylsilylferrocene carboxaldehyde **13** and alanine. The alanine resulting from decomposition of the oxazolidinones was treated with thionyl chloride and methanol. The resulting methyl ester was derivatised as a Mosher's amide, ^1H NMR spectroscopic analysis of which was consistent with it being homochiral. This rules out, at least in this example, the possibility of oxazolidinone decomposition via the corresponding enolate. The fact that *N*-pivaloyl alanine is not formed strongly suggests the decomposition pathway is via removal by the base of the pivaloyl group from the oxazolidinones followed by fragmentation of the resulting anion, presumably on work-up. Allylation is not observed because the enolate is never formed. Inspection of molecular models of **14** suggest that in these complexes the *t*-butyl group is sterically protecting the C-4 protons with the 2-ferrocenyl substituent preventing rotation of the pivaloyl to expose them as is believed to happen in the unsubstituted case [18].

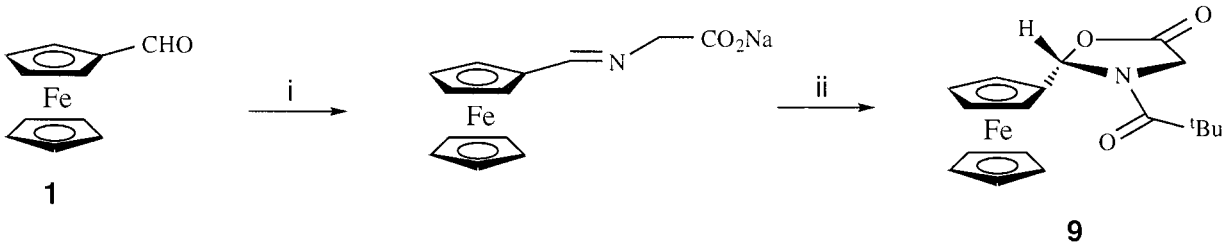
Other (OMe and PPh_2) 2-substituted ferrocene carboxaldehydes were also investigated with the same results as above.

3. Conclusion

In 2-ferrocenyl-3-pivaloyl-1,3-oxazolidin-5-ones the presence of a 2-substituent on the ferrocene ring exerts conformational restraints on the 3-pivaloyl group such that enolisation and hence C-4 alkylation is prevented.

4. Experimental

All reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. Tetrahydrofuran (THF) was distilled from Na/benzophenone and dichloromethane (CH_2Cl_2) dis-



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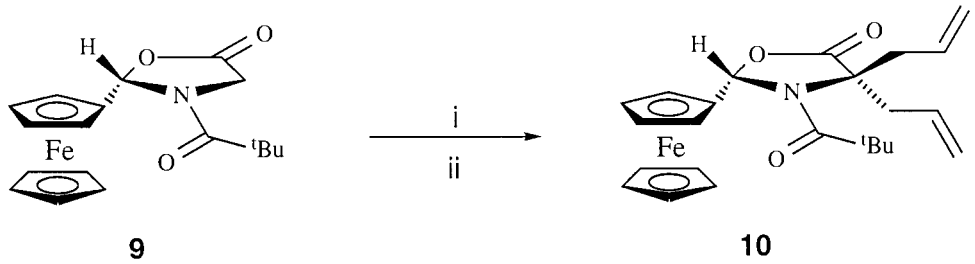
Scheme 3. Reagents and conditions: i, $H_2NCH_2CO_2Na$, absolute EtOH, 4Å molecular sieves, r.t.; ii, pivaloyl chloride, CH_2Cl_2, 4 Å molecular sieves, −18°C to r.t. overnight.



Scheme 4. Reagents and conditions: i, Allyl bromide; ii, 3 eq. KHMDS, 4 eq. 18-crown-6, THF, −78°C to r.t. overnight.

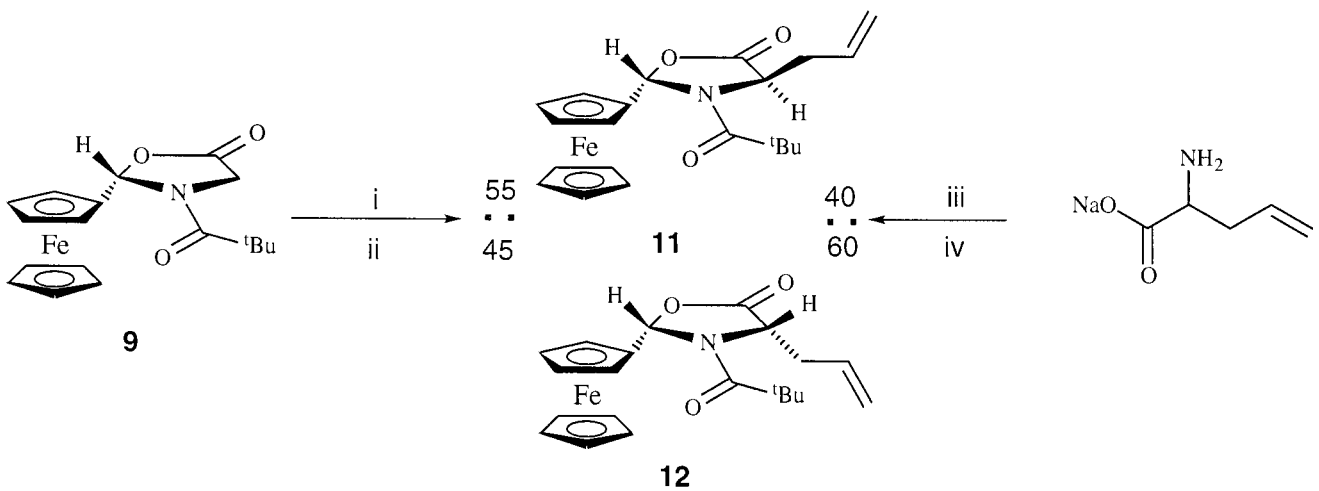
tilled from calcium hydride under a nitrogen atmosphere. All reactions were performed under a nitrogen atmosphere unless otherwise stated. The ^{1}H NMR spectra were performed on Bruker WH300, AM 500, AMX500 and Varian Gemini 200 instruments. Chemical shifts are reported in parts per million downfield relative to tetramethylsilane (δ 0.00); coupling constants are reported in hertz. Infrared spectra were obtained on a Perkin-Elmer 1750 FT spectrometer. Mass spectral data is reported as m/e (relative intensity). Elemental analyses were carried out by the Dyson Perrins Analytical Department.

4.1. General procedure for the preparation of ferrocenyl oxazolidinones

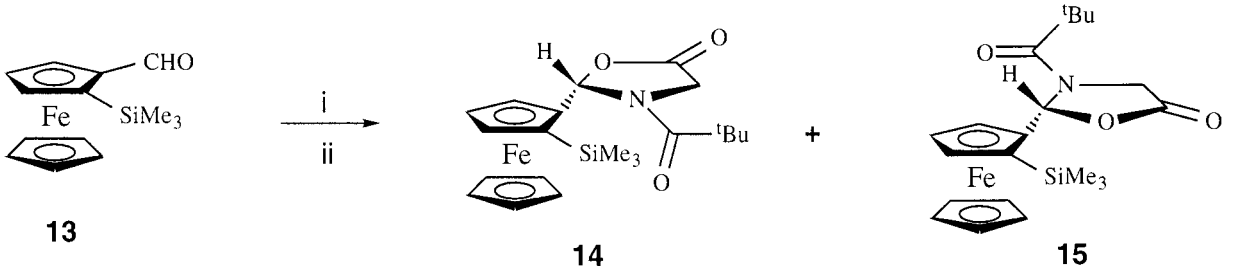
To the ferrocenyl aldehyde in ethanol over molecular sieves, was added sodium glycinate. The slurry was stirred for 16 h and then the solvent was removed in vacuo. The crude mixture of ferrocenyl imine was then suspended in dichloromethane and cooled to −18°C. Freshly distilled pivaloyl chloride as a solution in dichloromethane (2 ml) was added dropwise. The slurry was allowed to warm to room temperature over 16 h after which time the crude mixture was filtered through a plug of silica and the product crystallised from pentane.

4.2. Preparation of 2-ferrocenyl-3-pivaloyl-1,3-oxazolidin-5-one **9**

Following the general procedure, sodium glycinate (478 mg, 4.93 mmol) was added to ferrocenecarboxaldehyde **1** (1.160 g, 5.42 mmol) in ethanol (20 ml). Three hundred milligrams (1.02 mmol) of the resulting product was slurried in dichloromethane (10 ml) and treated with (188 μl, 1.53 mmol) of pivaloyl chloride. The desired product was obtained after washing with pentane (342 mg, 77% overall). ^{1}H NMR (300 MHz, C_6D_6): δ 6.92 (1 H, s, OCHN); 4.07 (5 H, s, 5 × HCp′); 4.54, 4.04, 3.88 (4 H, 3 s, 4 × HCp); 3.79, 3.57 (2H, m, CH_2); 0.80 ppm (9H, s, 3 × CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 175.1, 170.0 (OC=O, NC=O); 89.3 (NCHO); 69.2–64.7 (Cp); 69.1 (Cp′); 45.7 (CH_2); 39.0 ($C(CH_3)_3$); 26.9 (3 × CH_3). FTIR ν_{max} (KBr): 1784 (OC=O); 1630 cm^{-1} (NC=O). m/z (CI+): 356 (MH^+, 100%); 214 (FcCHO M^+, 78%). Anal. Found: C, 60.80; H, 5.83; N, 3.82. Calc.: C, 60.86; H, 5.96; N, 3.94.



Scheme 5. Reagents and conditions: i, Allyl bromide; ii, 1 eq. KHMDS, 1.5 eq. 18-crown-6, THF, −78°C to r.t. overnight; iii, ferrocenecarboxaldehyde **1**, absolute EtOH, 4 Å molecular sieves, r.t.; ii, pivaloyl chloride, CH_2Cl_2, 4 Å molecular sieves, −18°C to r.t. overnight.



Scheme 6. Reagents and conditions: i, $H_2NCH_2CO_2Na$, absolute EtOH, 4 Å molecular sieves, r.t.; ii, pivaloyl chloride, CH_2Cl_2, 4 Å molecular sieves, −18°C to r.t. overnight.

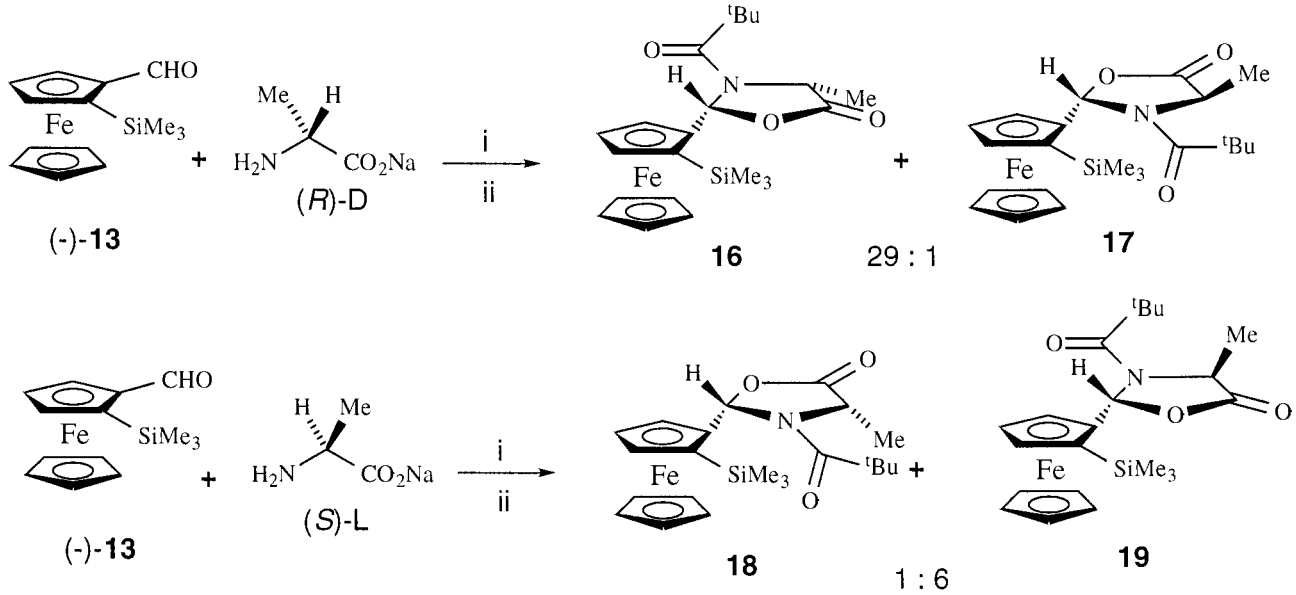
*4.3. Preparation of 4-allyl-2-ferrocenyl-3-pivaloyl-1,3-oxazolidin-5-one **11** and **12***

Following the general procedure, DL-sodium-2-amino-4-pentenoate (96 mg, 0.70 mmol) was added to ferrocenecarboxaldehyde **1** (150 mg, 0.70 mmol) in ethanol (10 ml). The resulting product was slurried in dichloromethane (10 ml) and treated with (87 μl, 0.70 mmol) of pivaloyl chloride. The desired product was obtained after washing with pentane (249 mg, 90%). The crude material was crystallised from diethylether to obtain the minor diastereomer with a diastereoselectivity of 135:3. The oil which remained contained the major diastereomer with a of 12:1. diastereoselectivity.

Major **12**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.05 (1H, s, OCHN); 5.92–5.79 (1H, m, C*H*=CH_2); 5.19–5.08 (2H, m, CH=C*H*$_2$); 4.61–4.55 (2H, m, 2 × HCp); 4.55–4.50 (1H, m, NCHCO); 4.22–4.12 (2H, m, 2 × HCp); 4.24 (5H, s, 5 × HCp′); 2.63–2.48 (2H, m, CH_2); 1.27 ppm (9H, s, 3 × CH_3). FTIR ν_{max} (KBr): 1793 (OC=O); 1641 cm^{-1} (NC=O). *m/z* (CI +): 396 (MH^+, 100%); 215 (FcCHO MH^+, 55%). minor **11**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.59 (1H, s, OCHN); 5.76–5.62 (1H, m, C*H*=CH_2); 5.23–5.17 (2H, m, CH=C*H*$_2$); 4.43, 4.20, 4.13 (4H, 3m, 4 × HCp); 4.72–4.70 (1H, dd, *J* = 2.6, 5.6, NCHCO); 4.26 (5H, s, 5 × HCp′); 3.00–2.91 (1H, m, CH_2); 2.73–2.66 (1H, m, CH_2); 1.10 ppm (9H, s, 3 × CH_3). FTIR ν_{max} (KBr): 1789 (OC=O); 1630 cm^{-1} (NC=O). *m/z* (CI +): 396 (MH^+, 100%); 215 (FcCHO MH^+, 87%). m.p. 108°C. Anal. Found: C, 63.98; H, 6.53; N, 3.64. Calc.: C, 63.81; H, 6.37; N, 3.54.

*4.4. Preparation of 5-bis allyl-2-ferrocenyl-3-pivaloyl-1,3-oxazolidin-5-one **10***

Oxazolidinone **9** (40 mg, 0.11 mmol) was dissolved in THF (5 ml) and cooled to −78°C. Allyl bromide (30 μl, 0.35 mmol, freshly distilled) was added to the solution. A premixed solution of 18-crown-6 (120 mg, 0.45 mmol, dried over molecular sieves as a THF solution) and KHMDS (0.68 ml, 0.34 mmol) was then



Scheme 7. Reagents and conditions: i, absolute EtOH, 4 Å molecular sieves, r.t.; ii, pivaloyl chloride, CH_2Cl_2, 4 Å molecular sieves, −18°C to r.t. overnight.

added dropwise by cannula as a solution in THF (2 ml). The solution was allowed to warm to room temperature over 16 h. The solvent was removed in vacuo and replaced by anhydrous diethyl ether. Anhydrous lithium chloride (200 mg) was added to the solution an stirred vigorously for 10 min. The slurry was filtered through a short plug of silica and the solvent concentrated in vacuo. The residue was crystallised from pentane to afford the title compound (29 mg, 61%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.59 (1H, s, OCHN); 6.05–5.97 (1H, m, C*H*=CH_2); 5.60–5.52 (1H, m, C*H*=CH_2); 5.28–5.21 (2H, m, CH=CH_2); 5.16–5.13 (2H, m, CH=CH_2); 4.42, 4.36, 4.29, 4.24 (4H, 4m, 4 × HCp); 4.28 (5H, s, 5 × HCp′); 3.32–3.37 (1H, dd, J = 9.1, 13.9, CHH); 3.15–3.13 (2H, m, CH_2); 2.56–2.52 (1H, dd, J = 5.9, 13.9, CHH); 1.04 ppm (9H, s, 3 × CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.4, 173.7 (OC=O, NC=O); 132.6, 131.5 (2 × *C*H=CH_2); 120.4, 119.4 (2 × CH=*C*H_2); 87.0 (OCHN); 73.4 (CO*C*CH_2); 69.1, 69.0, 68.7 (Cp); 69.3 (Cp′); 41.2 (*C*$(CH_3)_3$); 40.7, 37.8 (2 × CH_2); 28.5 (3 × CH_3). FTIR ν_{max} (KBr): 1790 (OC=O); 1646 cm^{-1} (NC=O). m/z (CI +): 435 (M^+, 30%). Anal. Found: C, 66.20; H, 6.85; N, 3.38. Calc.: C, 66.22; H, 6.71; N, 3.22.

4.5. Preparation of ortho substituted ferrocenecarboxaldehydes

Both racemic and enantioenriched 2-trimethylsilyl ferrocenecarboxaldehyde were prepared according to the literature procedure [18].

*4.6. 2-Trimethylsilyl ferrocenecarboxaldehyde **13***

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.04 (1H, s, CHO); 4.99 (1H, m, 5-HCp); 4.73 (1H, t, J 2.5, 4-HCp); 4.54 (1H, m, 3-HCp); 4.27 (5H, s, 5 × HCp′); 0.33 (9H, s, 3 × CH_3); m/z (EI): 286 (M^+, 69%); 271 (100%); 207 (72%).

*4.7. Preparation of 2-(2-trimethylsilyl ferrocenyl)-3-pivaloyl-1,3-oxazolidin-5-one **14***

Following the general procedure, sodium glycinate (24 mg, 0.25 mmol) was added to aldehyde **13** (72 mg, 0.25 mmol) in ethanol (10 ml). The resulting product was slurried in dichloromethane (10 ml) and treated with (31 μl, 0.25 mmol) of pivaloyl chloride. The desired product was obtained after washing with pentane (64 mg, 60%) and showed a diastereoselectivity of 2:1. Fractional crystallisation allowed isolation of material with a d.r. of 10:1.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (1H, s, OCHN); 4.22 (5H, s, 5 × HCp′); 4.75, 4.32, 4.11 (3H, 3 × HCp); 4.16 (2H, m, CH_2); 1.39 ppm (9H, s, 3 × CH_3). FTIR ν_{max} (KBr): 1800 (OC=O), 1653 cm^{-1} (NC=O). m/z (CI +): 428 (MH^+, 100%); 287 (47%). Anal. Found: C, 59.13; H, 6.97; N, 3.16. Calc.: C, 59.02; H, 6.84; N, 3.28.

Acknowledgements

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