Asymmetric synthesis of β-lactams and pseudopeptides *via* stereoselective conjugate additions of lithium (α-methylbenzyl)-allylamide to α,β-unsaturated iron acyl complexes

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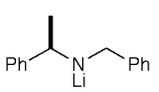
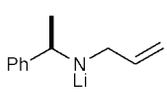
Lithium (α-methylbenzyl)allylamide **2** undergoes stereoselective conjugate additions to α,β-unsaturated iron acyl complexes **3a**–**c** to afford β-amino iron acyl adducts **5a**–**c** and **6a**–**c**. These adducts may be deallylated smoothly using palladium(0) catalysis providing the corresponding homochiral secondary amines **7a**–**c** which, upon oxidative decomplexation with bromine or *N*-bromosuccinimide, undergo direct β-lactam ring formation. The diastereoselectivity for the conjugate addition to **3a** may be further improved by the use of magnesium amide **10**. Oxidative decomplexation of one of the β-amino iron acyl adducts **5b** in the presence of α-amino esters provides pseudopeptide fragments comprising an α-amino acid coupled to a β-amino acid.

Introduction

β-Amino acids and their derivatives are currently of enormous interest[1] owing to their occurrence in biologically active peptides, their importance as precursors to β-lactams and their role in determining secondary structure within synthetic β-peptides.[2] As a consequence, many methods have been developed for their asymmetric synthesis.[3] In particular, the stereoselective conjugate addition of homochiral secondary lithium amide reagents to α,β-unsaturated esters provides an extremely efficient method for the asymmetric synthesis of β-amino acid derivatives.[4–8] Lithium (α-methylbenzyl)benzylamide **1** has proved to be an excellent homochiral ammonia



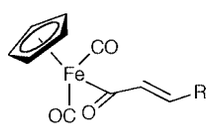
(*R*)-**1**



(*R*)-**2**

equivalent for this process.[5] Its use is however limited by subsequent deprotection through hydrogenolysis, which is often incompatible with many important functional groups and although procedures for the selective removal of just one of the *N*-benzyl groups may be achieved,[6] it can be problematic. As a consequence, lithium (α-methylbenzyl)allylamide **2** has been developed as a differentially protected homochiral ammonia equivalent.[7] The *N*-allyl group may be selectively removed under rhodium or palladium catalysis to reveal the secondary amine which may be utilized in further transformations. The use of lithium amide **2** in conjugate additions to α,β-unsaturated esters has led to the development of procedures for accessing homochiral β-lactams and other β-amino acid derivatives.[8]

Chiral α,β-unsaturated acyl–iron complexes have been shown to be good acceptors for 1,4-addition reactions using metallated nitrogen nucleophiles,[9] and β-amino–iron acyl complexes are well known to undergo oxidative decomplexation *via* an activated iron acyl species which is intramolecularly trapped to afford β-lactams.[9,10] We now wish to report the results of our investigations into the conjugate addition of lithium amide (*R*)-**2** to prochiral (*E*)-α,β-unsaturated acyl(cyclopentadienyl)-dicarbonyliron[11] complexes **3a**–**c**. Subsequent selective removal of the *N*-allyl group in the adduct would lead to a system in which oxidative decomplexation conditions should bring about

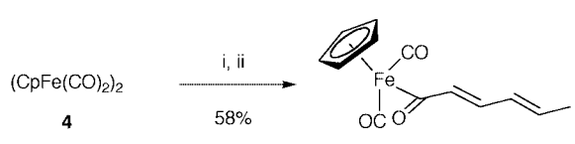


3a R=CH_3
3b R=Ph
3c R=(*E*)-propenyl

direct β-lactam ring formation. Furthermore, oxidative decomplexation of the doubly protected adducts in the presence of an α-amino ester should lead to direct peptide coupling to a β-amino acid derivative to generate a pseudopeptide fragment. Both methodologies would therefore obviate the need for multi-step amide bond forming procedures required for ordinary β-amino ester systems.

Results and discussion

α,β-Unsaturated iron acyl complexes **3a**–**c** were chosen as acceptor substrates. Complex **3c** was synthesized according to the known procedure for the synthesis of complexes **3a** and **3b**.[12] Complex **3c** was synthesized in similar fashion by the reductive cleavage of readily available cyclopentadienyldicarbonyliron dimer **4** using sodium amalgam to afford the cyclopentadienyldicarbonyliron anion, which upon treatment with (*E*,*E*)-sorboyl chloride at −78 °C gave complex **3c** in 58% yield after work up and chromatography (Scheme 1).



4 **3c**

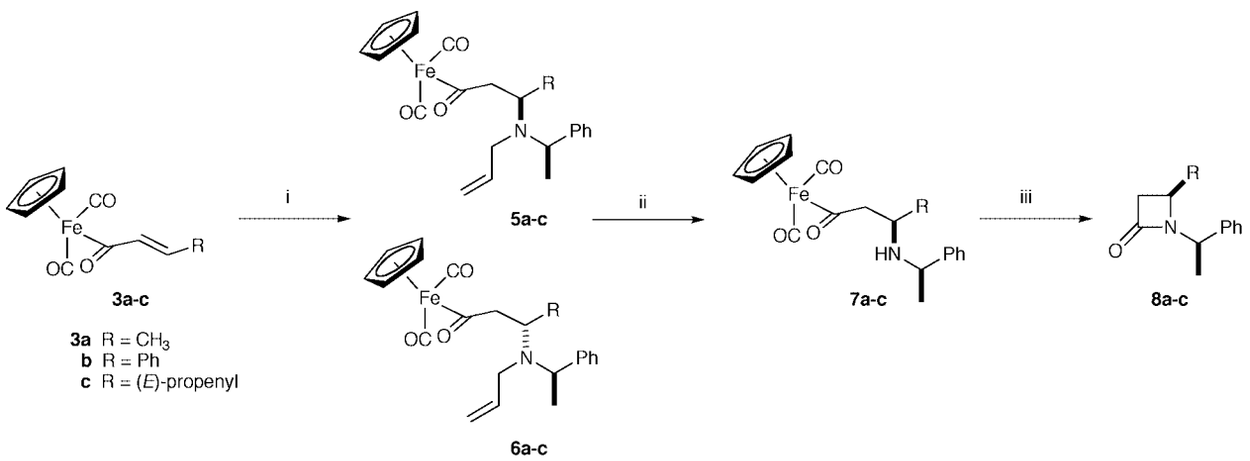
Scheme 1 *Reagents and conditions*: (i) Na–Hg, THF; (ii) (*E*,*E*)-sorboyl chloride, THF, −78 °C.

Conjugate addition of homochiral lithium amide (*R*)-**2** to the complexes **3a**–**c** was carried out by slow addition of a THF solution of (*R*)-**2** to the requisite complex in THF at −100 °C and warming to −78 °C. Performing the addition at −78 °C led to destruction of the intermediate ferra–enolate adduct. The conjugate additions proceeded with good diastereoselectivities (82 : 18–95 : 5) to afford the β-amino iron acyl complexes **5/6a**–**c** as inseparable mixtures of diastereoisomers in moderate yields (54–67%) (Scheme 2, Table 1).[13]

Table 1 Diastereoselectivities in the addition of (*R*)-**2** to **3a–c** (Scheme 2)

R	**5**:**6** ds[a] (Yield %)	**7** de[b] (Yield %)	**8** $[\alpha]_D^{22}$ ($CHCl_3$); (Yield %)
CH_3 (**a**)	82:18 (67)	>95% (77)	+64.2 (*c* 0.95); (43)
Ph (**b**)	95:5 (61)	>95% (90)	+57.9 (*c* 1.06); (41)
(*E*)-CH_3CH=CH (**c**)	84:16 (54)	>95% (76)	−39.4 (*c* 1.02); (51)

[a] Determined by 500 MHz ^{1}H NMR. [b] Determined by 200 MHz ^{1}H NMR.



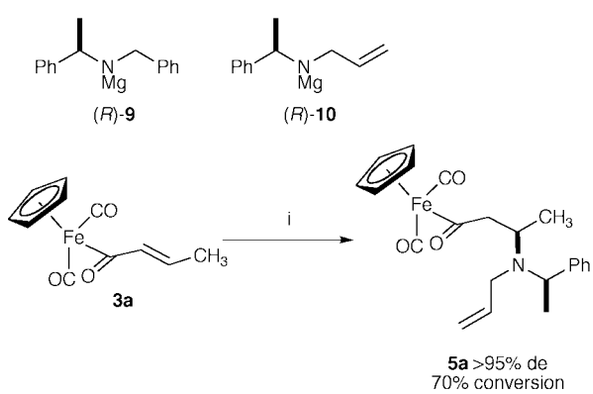
Scheme 2 *Reagents and conditions*: (i) (*R*)-**2**, THF, −100 °C to −78 °C; (ii) $Pd(PPh_3)_4$, NDMBA, CH_2Cl_2, 35 °C, then chromatography; (iii) for **7a** and **7b** Br_2, CH_2Cl_2, −78 °C, then Et_3N; for **7c** NBS, CH_2Cl_2, −78 °C, then Et_3N.

Attempts to carry out the deallylation of complexes **5/6a–c** were unsatisfactory using Wilkinson's catalyst,[14] since the elevated temperatures required led to significant decomposition of the starting materials and products. Deallylation of the adducts was best effected by treatment of the diastereomeric mixtures with a catalytic amount of tetrakis(triphenylphosphine)-palladium(0) and *N*,*N*′-dimethylbarbituric acid (NDMBA) in dichloromethane at 35 °C.[15] The deallylated complexes **7a–c** were obtained as single diastereoisomers (de >95%) in excellent yields (76–90% from the respective diastereomeric mixtures), since the more polar minor diastereoisomers could be separated by chromatography.

Complexes **7a** and **7b** underwent oxidative decomplexation using bromine in dichloromethane at −78 °C to afford the desired diastereomerically pure homochiral β-lactams **8a** and **8b** in yields of 43 and 41% respectively (Scheme 2). Complex **7c** was converted to homochiral β-lactam **8c** using *N*-bromosuccinimide as the oxidant in 51% yield.

Homochiral β-lactams ***ent*-8a–c** bearing the same relative stereochemistry, but opposite absolute stereochemistry, have previously been synthesized[7] and a comparison showed them to possess identical ^{1}H NMR spectra and specific rotations of the same magnitude and opposite sign. Apart from confirming them as enantiomers, this also allowed the assignment of the absolute configurations of the newly formed stereogenic centres in complexes **5a–c** and **6a–c**, with the sense of induction being that as expected from previous studies for the additions of lithium amides **1** and **2** to simple α,β-unsaturated esters.[5]

Although the conjugate additions to the α,β-enoyl iron systems had indeed proceeded with high diastereoselectivity, the levels of selectivity observed were somewhat lower than expected from studies on additions to α,β-unsaturated esters.[5,7,8] In an attempt to increase selectivity, the additions were performed using magnesium as a more strongly coordinating cation. The magnesium amide **9** has recently been shown to undergo highly diastereoselective conjugate additions to α,β-unsaturated esters,[16] with the asymmetric induction occurring in the same sense as in the case of lithium amides. Their reactivity is much lower however, with additions requiring a larger excess of the amide and longer reaction times. Addition of 4.2 equivalents of magnesium amide (*R*)-**10** to iron complex **3a** in THF at −78 °C resulted in the formation of β-amino iron acyl complex **5a** in >95% de and 70% conversion (by inspection of the crude 200 MHz ^{1}H NMR spectrum) (Scheme 3).

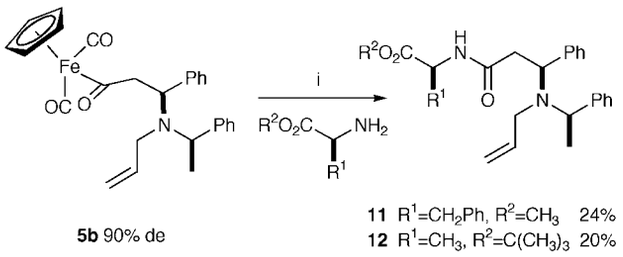


Scheme 3 *Reagents and conditions:* (i) (*R*)-**10**, THF, −78 °C.

Under the same conditions, complexes **3b** and **3c** failed to undergo conjugate addition of the magnesium amide, presumably due to a combination of the greater stability of these extended conjugated systems and reduced nucleophilicity of the magnesium amide relative to the analogous lithium amide.

Finally, decomplexation of the doubly protected complex **5b** (90% de) using *N*-bromosuccinimide in the presence of L-α-amino esters; phenylalanine methyl ester or alanine *tert*-butyl ester afforded the protected β-phenylalanine pseudopeptide fragments **11** and **12** after work up and chromatography, as single diastereoisomers in unoptimized yields of 24 and 20% respectively (Scheme 4).

In summary, we have demonstrated an asymmetric synthesis of β-amino acid derivatives *via* stereoselective conjugate additions of a differentially protected lithium amide to α,β-unsaturated iron acyl complexes. The iron acyl moiety may be activated directly towards amide bond formation leading to homochiral β-lactams and pseudopeptide fragments.



Scheme 4 *Reagents and condition*: (i) NBS, −42 to 25 °C.

Experimental

General experimental

All experiments and purifications involving organometallic complexes and reagents were carried out using an atmosphere of dry nitrogen. Standard vacuum line, Schlenk and cannula techinques were used throughout. Solvents were deoxygenated prior to use by repeated evacuation–purge cycles. Procedures involving organic compounds required no special conditions, unless otherwise stated. THF was distilled, under an atmosphere of dry nitrogen, from sodium benzophenone ketyl; dichloromethane was distilled from calcium hydride also under dry nitrogen. Petrol refers to that fraction of petroleum ether which boils in the range 40–60 °C and was redistilled before use. All other solvents were used as supplied, without prior purification. Butyllithium was used as a solution in hexanes at the molarity stated and methylmagnesium bromide was used as a 3.0 M solution in diethyl ether. Triethylamine was distilled, under a nitrogen atmosphere, from calcium hydride and stored over potassium hydroxide pellets.

Tetrakis(triphenylphosphine)palladium(0) was recrystallized from dichloromethane under an atmosphere of nitrogen and *N*-bromosuccinimide was recrystallized from water, both were stored in the absence of light. All other reagents were used as supplied, without prior purification. Flash chromatography was performed on silica gel (Kieselgel 60) and alumina (grade I). Melting points were recorded using a Gallenkamp hot stage apparatus and are uncorrected. NMR spectra were recorded using deuteriochloroform as solvent on a Varian Gemini 200 (^{1}H; 200 MHz and ^{13}C; 50.32 MHz) instrument. 500 MHz NMR spectra were recorded on a Bruker AM500 (^{1}H; 500.13 MHz and ^{13}C; 125.77 MHz) instrument. All chemical shifts (δ) are given in ppm and coupling constants (J) in Hz. Mass spectra were recorded using chemical ionization (CI) on a VG MASS LAB 20-250 or fast atom bombardment (FAB) on a VG MICROMASS ZAB-1F instrument. Infrared spectra were recorded on a Perkin-Elmer 1750 Fourier Transform spectrometer using either chloroform solutions in 0.1 mm NaCl cells, KBr discs or thin films. For clarity only the salient, characteristic peaks are noted. Elemental analyses were obtained by the Dyson Perrins analytical department. Optical rotations were recorded on Perkin-Elmer 241 polarimeter and are given in 10^{-1} deg cm^2 g^{-1}.

(*E*,*E*)-Hexa-2,4-dienoyl(cyclopentadienyl)dicarbonyliron 3c

A 1% sodium amalgam was prepared by the slow addition of small portions of sodium metal (1.84 g) to dry mercury (13.5 cm^3, 184 g) with stirring under a nitrogen atmosphere (some initial heating was required). After the addition was complete the amalgam was allowed to cool. THF (100 cm^3) was transferred to the amalgam *via* cannula and $[(\eta^5\text{-}C_5H_5)Fe(CO)_2]_2$ **4** (7.0 g, 24.4 mmol) added as a solid to the THF–amalgam mixture. The resulting purple solution was stirred vigorously above the amalgam for 4 h at ambient temperature, by which time the solution had become an orange–brown colour. This solution was transferred to a dry flask *via* cannula. The stirred solution of $[(\eta^5\text{-}C_5H_5)Fe(CO)_2]^-Na^+$, at −78 °C, was treated with (*E*,*E*)-hexa-2,4-dienoyl chloride (7.9 g, 61.0 mmol); neat *via* syringe. The resulting solution was allowed to warm to ambient temperature over 0.5 h and stirred for a further 24 h with subsequent removal of solvent *in vacuo*. The residue was redissolved in dichloromethane and filtered through a plug of alumina (grade IV). The filtrate was concentrated *in vacuo* to give the crude mixture, which was subjected to flash chromatography on silica gel [15% ethyl acetate–petrol; R_f 0.30] to give the title compound as an orange oil. Crystallization [diethyl ether–hexane; 6:1, −30 °C] gave orange crystals (7.77 g, 58%); mp 59–61 °C (Found: C, 57.7; H, 4.3. $C_{13}H_{12}FeO_3$ requires C, 57.4; H, 4.45%); ν_{max}($CHCl_3$)/cm^{-1} 2017vs, 1942vs (C≡O), 1642s (C=O), 1613s, 1566s (C=C); δ_H(200 MHz; $CDCl_3$) 6.36–5.95 (4H, m, C*H*=C*H*–C*H*=C*H*), 4.88 (5H, s, Cp), 1.83 (3H, d, J 5.4, CH_3); δ_C(50 MHz; $CDCl_3$) 140.24 (CO*C*H), 139.97 (COCH=C*H*), 130.64 (CH=C*H*CH$_3$), 86.41 (Cp), 18.76 (CH_3); *m*/*z* (FAB) 273 (MH^+, 100%).

General procedure 1—lithium amide additions

A stirred solution of (α-methylbenzyl)allylamine[7] (2.6 eq.) in THF (approx. 1 mmol cm^{-3}) at −78 °C was treated with 1.5 M butyllithium (2.2 eq.). The resulting yellow solution was stirred for 1 h and then added dropwise *via* cannula over 0.5 h to a stirred solution of the α,β-enoyliron complex (1 eq.) in THF (approx. 1 mmol cm^{-3}) at −100 °C. The resulting dark solution was allowed to warm to −78 °C over 0.5 h, stirred for a further 4 h and subsequently quenched by the addition of methanol (4 cm^3). The mixture was allowed to warm to ambient temperature and the solvent removed *in vacuo*. The residue was redissolved in dichloromethane and filtered through a plug of alumina (grade IV). The filtrate was concentrated *in vacuo* to give the crude material as a dark red–brown oil which was purified as necessary.

General procedure 2—deallylation reactions

A solution of the β-aminoalkanoyliron complex (1 eq.) in dichloromethane (approx. 0.25 mmol cm^{-3}) was added, *via* cannula, to a stirred solution of NDMBA (3 eq.) and tetrakis(triphenylphosphine)palladium(0) (1 mol%) in dichloromethane at 35 °C. The solution was stirred for 1.5 h and then allowed to cool to ambient temperature with subsequent removal of solvent *in vacuo*. The residue was redissolved in diethyl ether and washed with saturated aqueous sodium bicarbonate (×2). The organic layer was then filtered through a plug of magnesium sulfate and alumina (grade IV) and the filtrate concentrated *in vacuo* to give the crude material which was purified as necessary.

General procedure 3—bromine decomplexations

A stirred solution of the β-aminoalkanoyliron complex (1 eq.) in dichloromethane (approx. 0.25 mmol cm^{-3}), precooled to −78 °C, was treated with bromine (2 eq.). The mixture was stirred for 1 h and triethylamine (6 eq.) was added. The resulting solution was allowed to warm to ambient temperature whilst stirring and the solvent was removed *in vacuo*. The residue was redissolved in diethyl ether and filtered through a plug of magnesium sulfate and alumina (grade IV). The filtrate was concentrated *in vacuo* to give the crude material which was purified as necessary.

{(3*R*/*S*)-3-[*N*-(1*R*)-1-Phenylethyl-*N*-(prop-2-enyl)amino]-butanoyl}(cyclopentadienyl)dicarbonyliron 5a/6a

Complexes **5a/6a** were prepared from complex **3a** (1.0 g, 4.1 mmol) and (α-methylbenzyl)allylamine (1.70 g, 10.6 mmol) in accordance with general procedure 1. The crude material was subjected to flash chromatography on silica gel [20% ethyl acetate–1% NH_3(aq)–petrol; R_f 0.30] to afford the title compound as an orange oil (1.10 g, 67%), an inseparable mixture of

diastereoisomers; **5a**:**6a** 82:18 by the 500 MHz ^{1}H NMR spectrum of the crude material (Found: C, 65.1; H, 6.4; N, 3.7. $C_{27}H_{27}FeNO_3$ requires C, 64.9; H, 6.2; N, 3.4%); ν_{max}(thin film)/cm^{-1} 2012vs, 1952vs (C≡O), 1651vs, 1646vs (C=O); δ_H(200 MHz; $CDCl_3$) (3*R*,1′*R*)-**5a**;[13] 7.37–7.21 (5H, m, Ph), 5.94–5.75 (1H, m, NCH_2CH=CH_2), 5.22–5.02 (2H, m, NCH_2CH=CH_2), 4.72 (5H, s, Cp), 3.91 (1H, q, *J* 6.8, PhC*H*(CH_3)N), 3.42 (1H, ABX system; X part, ddq, *J* 6.8, J_{AX} 4.9, J_{BX} 1.5, CH_3CHCH_2), 3.15 (2H, m, NCH_2CH=CH_2), 2.84, 2.81 (2H, ABX system; AB part, J_{AX} 4.9, J_{BX} 1.5, J_{AB} 14.5, CH_3CHCH_2), 1.35 (3H, d, *J* 6.8, PhCH(CH_3)N), 0.97 (3H, d, *J* 6.8, CH_3CHCH_2); [(3*S*,1′*R*)-**6a**;[13] δ_H(200 MHz; $CDCl_3$) 7.37–7.15 (5H, m, Ph), 5.94–5.75 (1H, m, NCH_2-CH=CH_2), 5.22–5.02 (2H, m, NCH_2CH=CH_2), 4.82 (5H, s, Cp), 3.91 (1H, q, *J* 6.8, PhC*H*(CH_3)N), 3.42 (1H, ABX system; X part, m CH_3CHCH_2), 3.15 (2H, m, NCH_2CH=CH_2), 3.26–2.79 (2H, ABX system; AB part, J_{AX} 8.2, J_{BX} 4.3, J_{AB} 16.0, CH_3CHCH_2), 1.35 (3H, d, *J* 6.8, PhCH(CH_3)N), 0.78 (3H, d, *J* 6.8, CH_3CHCH_2)]; δ_C(50 MHz; $CDCl_3$) 145.3 (Ph: C_{ipso}), 139.4 (*C*H=CH_2), 128.3, 127.8 (Ph: $C_{metalortho}$), 126.8 (Ph: C_{para}), 115.5 (CH_2=CH), 86.3 (Cp), 72.4 (CH_2CO), 58.2, 49.3 (N*C*H), 49.8 (NCH_2), 19.2, 18.0 (CH_3); *m*/*z* (CI) 408 (MH$^+$, 100%).

{(3*S*/*R*)-3-[*N*-(1*R*)-1-Phenylethyl-*N*-(prop-2-enyl)amino]-3-phenylpropanoyl}(cyclopentadienyl)dicarbonyliron 5b/6b

Complexes **5b**/**6b** were prepared from complex **3b** (1.0 g, 3.25 mmol) and (α-methylbenzyl)allylamine (1.31 g, 8.10 mmol) in accordance with general procedure 1. The crude material was subjected to flash chromatography on silica gel [10% ethyl acetate–petrol; R_f 0.35] to afford the title compound as an orange oil (0.93 g, 61%), an inseparable mixture of diastereoisomers; **5b**/**6b** 95:5 by 500 MHz ^{1}H NMR spectrum of the crude material (Found: C, 69.2; H, 6.0; N, 2.9. $C_{27}H_{27}FeNO_3$ requires C, 69.1; H, 5.8; N, 3.0%); ν_{max}($CHCl_3$)/cm^{-1} 2012vs, 1962vs (C≡O), 1641vs (C=O); δ_H(200 MHz; $CDCl_3$) (3*S*,1′*R*)-**5b**; 7.41–7.19 (10H, m, Ph) 5.93–5.74 (1H, m, NCH_2C*H*=CH_2), 5.20–5.01 (2H, m, NCH_2CH=CH_2), 4.56 (5H, s, Cp), 4.46 (1H, ABX system; X part, dd, J_{AX} 9.5, J_{BX} 3.9, CH_2CHPh), 3.96 (1H, q, *J* 7.0, PhC*H*(CH_3)N), 3.50, 3.18 (2H, ABX system; AB part, J_{AX} 9.5, J_{BX} 3.9, J_{AB} 16.8, CH_2CHPh), 3.08 (2H, m, NCH_2CH=CH_2), 1.24 (3H, d, *J* 7.0, PhCH(CH_3)N); [(3*R*,1′*R*)-**6b**; 4.62 (5H, s, Cp)]; δ_C(50 MHz; $CDCl_3$) 144.9 (Ph: C_{ipso}), 143.5 (Ph: C_{ipso}), 139.8 (*C*H=CH_2), 128.4, 128.3, 128.0, 127.8, 127.0, 126.8 (Ph), 115.6 (CH_2=CH), 86.2 (Cp), 70.8 (CH_2CO), 58.7, 56.0 (N*C*H), 50.0 (NCH_2), 15.1 (CH_3); *m*/*z* (FAB) 470 (MH$^+$, 5%).

{(3*S*/*R*)-3-[*N*-(1*R*)-1-Phenylethyl-*N*-(prop-2-enyl)amino]-(*E*)-hex-4-enoyl}(cyclopentadienyl)dicarbonyliron 5c/6c

Complexes **5c**/**6c** were prepared from complex **3c** (1.0 g, 3.67 mmol) and (α-methylbenzyl)allylamine (1.48 g, 9.20 mmol) in accordance with general procedure 1. The crude material was subjected to flash chromatography on silica gel [20% ethyl acetate–1% NH_3(aq)–petrol; R_f 0.35]. The resulting mixture was further purified by chromatography on alumina (grade I) [15% diethyl ether–petrol; R_f 0.40] to afford the title compound as an orange oil (0.86 g, 54%), an inseparable mixture of diastereoisomers; **5c**:**6c** 84:16 by 500 MHz ^{1}H NMR spectroscopy of the crude material (Found: C, 66.5; H, 6.15. $C_{27}H_{27}FeNO_3$ requires C, 66.5; H, 6.3%); ν_{max}(thin film)/cm^{-1} 2012vs, 1952vs (C≡O), 1651vs (C=O); δ_H(200 MHz; $CDCl_3$) (3*S*,1′*R*)-**5c**; 7.39–7.21 (5H, m, Ph), 5.92–5.72 (1H, m, NCH_2C*H*=CH_2), 5.46–5.41 (2H, m, C*H*=C*H*CH_3), 5.28–5.01 (2H, m, NCH_2CH=CH_2), 4.74 (5H, s, Cp), 3.97 (1H, q, *J* 6.9, PhC*H*(CH_3)N), 3.87 (1H, ABX system; X part, ddd, *J* 4.4, J_{AX} 8.0, J_{BX} 4.5, CH_2CHCH=CH), 3.12–3.10 (2H, m, NCH_2-CH=CH_2), 3.04, 2.89 (2H, ABX system; AB part, J_{AX} 8.0, J_{BX} 4.5, J_{AB} 16.0, CH_2CHCH=CH), 1.69 (3H, d, *J* 3.6, CH=CHC*H*$_3$), 1.35 (3H, d, *J* 6.9, PhC*H*(CH_3)N); [(3*R*,1′*R*)-**6c**; 4.77 (5H, m, Cp)]; δ_C(50 MHz; $CDCl_3$) 145.4 (Ph: C_{ipso}), 128.3, 127.8 (Ph: $C_{metalortho}$), 126.7, 126.6 (Ph: C_{para}/CH_3CH=CH), 139.4, 131.8 (CH*C*H=CHCH$_3$/NCH$_2$*C*H=CH$_2$), 115.7 (CH_2=CH), 86.3 (Cp), 70.1 (CH_2CO), 57.0, 55.4 (N*C*H), 50.0 (CH_2N), 18.5, 17.9 (CH_3); *m*/*z* (CI) 434 (MH$^+$, 100%).

Magnesium amide addition of (*R*)-10 to complex 3a

A stirred solution of (α-methylbenzyl)allylamine (737 mg, 4.5 mmol), in THF (5 cm^3) at 0 °C, was treated with 3.0 M methylmagnesium bromide (1.4 cm^3, 4.1 mmol). The resulting yellow solution was stirred for 1 h and subsequently cooled to −78 °C. Complex **3a** (250 mg, 1.0 mmol) was added dropwise *via* cannula to the stirred magnesium amide as a THF solution. The resulting solution was stirred at −78 °C for 16 h and quenched by the addition of methanol (4 cm^3). The mixture was allowed to warm to ambient temperature with subsequent removal of solvent *in vacuo*. The residue was dissolved in dichloromethane and filtered through a plug of alumina (grade IV) and the filtrate concentrated *in vacuo* to give the crude material as an orange oil. Spectroscopic analysis of the crude mixture indicated an approximately 70% conversion to adduct (3*R*,1′*R*)-**5a** with the minor diastereoisomer[13] (3*S*,1′*R*)-**6a** not observable in the 200 MHz ^{1}H NMR spectrum.

{(3*R*)-3-[*N*-(1*R*)-1-Phenylethylamino]butanoyl}(cyclopentadienyl)dicarbonyliron 7a

Complex **7a** was prepared from complex **5a** (230 mg, 0.56 mmol, 64% de), NDMBA (270 mg, 1.69 mmol) and tetrakis(triphenylphosphine)palladium(0) (7 mg, 5.6 μmol) in accordance with general procedure 2. The crude material was subjected to flash chromatography on silica gel [40% ethyl acetate–1% NH_3(aq)–petrol; R_f 0.35] affording the title compound as an orange oil (125 mg, 76%), this was shown to be >95% de by 200 MHz ^{1}H NMR spectroscopy (94% yield based on 64% de of starting material) (Found: C, 62.4; H, 5.4; N, 4.1. $C_{19}H_{21}FeNO_3$ requires C, 62.1; H, 5.8; N, 3.8%); ν_{max}($CHCl_3$)/cm^{-1} 2010vs, 1955vs (C≡O), 1635s (C=O); δ_H(200 MHz; $CDCl_3$) 7.33–7.20 (5H, m, Ph), 4.86 (5H, s, Cp), 3.81 (1H, q, *J* 6.6, NC*H*(CH_3)Ph), 3.14, 2.98 (2H, ABX system; AB part, J_{AX} 7.4, J_{BX} <1.5, J_{AB} 12.2, CH_2CHCH_3), 2.98 (1H, ABX system; X part, J_{AX} 7.4, J_{BX} <1.5, *J* 6.0, CH_2CHCH_3), 1.32 (3H, d, *J* 6.6, NCH(CH_3)Ph), 0.96 (3H, d, *J* 6.0, CH_2-$CHCH_3$); δ_C(50 MHz; $CDCl_3$) 146.7 (Ph: C_{ipso}), 128.5, 126.9, 126.7 (Ph), 86.4 (Cp), 74.2 ($COCH_2$), 54.8, 46.9 (N*C*H), 25.2, 18.9 (CH_3); *m*/*z* (FAB) 368 (MH$^+$, 35%).

{(3*S*)-3-[*N*-(1*R*)-1-Phenylethylamino]-3-phenylpropanoyl}-(cyclopentadienyl)dicarbonyliron 7b

Complex **7b** was prepared from complex **5b** (391 mg, 0.84 mmol, 90% de), NDMBA (394 mg, 2.52 mmol) and tetrakis(triphenylphosphine)palladium(0) (10 mg, 8.4 μmol) in accordance with general procedure 2. The crude material was subjected to flash chromatography on silica gel [35% ethyl acetate–1% NH_3(aq)–petrol; R_f 0.35] affording the title compound as an orange oil (319 mg, 90%), this was shown to be >95% de by 200 MHz ^{1}H NMR spectroscopy (95% yield based on 90% de of starting material) (Found: C, 67.3; H, 5.4; N, 3.5. $C_{24}H_{23}FeNO_3$ requires C, 67.15; H, 5.4; N, 3.3%); ν_{max}($CHCl_3$)/cm^{-1} 2022vs, 1963vs (C≡O), 1636s (C=O); δ_H(200 MHz; $CDCl_3$) 7.35–7.15 (10H, m, Ph), 4.71 (5H, s, Cp), 4.21 (1H, ABX system; X part, dd, J_{AX} 6.4, J_{BX} 6.4, CH_2CHPh), 3.57 (1H, q, *J* 6.6, NC*H*(CH_3)Ph), 3.30 (2H, ABX system; AB part, J_{AX} 6.4, J_{BX} 6.4, J_{AB} <1.5, CH_2CHPh), 1.34 (3H, d, *J* 6.6, NCH(CH_3)Ph); δ_C(50 MHz; $CDCl_3$) 146.41, 143.69 (Ph: C_{ipso}), 128.6, 128.6, 127.5, 127.2, 126.9, 126.74 (Ph), 86.3 (Cp), 73.9 ($COCH_2$), 56.9, 55.0 (N*C*H), 21.6 (CH_3); *m*/*z* (FAB) 430 (MH$^+$, 22%).

{(3*S*)-3-[*N*-(1*R*)-1-Phenylethylamino]-(*E*)-hex-4-enoyl}(cyclopentadienyl)dicarbonyliron 7c

Complex **7c** was prepared from complex **5c** (300 mg, 0.69 mmol, 68% de), NDMBA (325 mg, 2.07 mmol) and tetrakis(triphenylphosphine)palladium(0) (10 mg, 6.9 μmol) in accordance with general procedure 2. The crude material was subjected to flash chromatography on silica gel [45% ethyl acetate–1% NH_3(aq)–petrol; R_f 0.35] affording the title compound as an orange oil (207 mg, 76%); this was shown to be >95% de by 200 MHz ^{1}H NMR spectroscopy (90% yield based on 68% de of starting material) (Found: C, 64.4; H, 6.2; N, 3.8. $C_{21}H_{23}FeNO_3$ requires C, 64.1; H, 5.9; N, 3.6%); ν_{max}($CHCl_3$)/cm^{-1} 2022vs, 1963vs (C≡O), 1636m (C=O); δ_H(200 MHz; $CDCl_3$) 7.30–7.15 (5H, m, Ph), 5.50 (1H, dq, *J* 6.3, 15.5, (*E*)-CHCH=C*H*CH$_3$), 5.19 (1H, ddq, *J* 1.5, 7.7, 15.5, (*E*)-CHC*H*=CHCH$_3$), 4.85 (5H, s, Cp), 3.74 (1H, q, *J* 6.5, NC*H*(CH$_3$)Ph), 3.48 (1H, ABX system; X part, ddd, *J* 7.7, J_{AX} 7.7, J_{BX} 7.7, CH$_2$C*H*CH=CH$_2$), 3.09 (2H, ABX system; AB part, m, C*H*$_2$CHCH=CH$_2$), 1.61 (3H, d, *J* 6.3, CH=CHC*H*$_3$), 1.31 (3H, d, *J* 6.5, NCH(C*H*$_3$)Ph); δ_C(50 MHz; $CDCl_3$) 146.7 (Ph: C$_{ipso}$), 133.5 (CH$_3$*C*H=CH), 128.5, 126.8, 126.6 (Ph/CH$_3$CH=*C*H), 86.4 (Cp), 71.9 (CO*C*H$_2$), 55.4, 54.8 (N*C*H), 22.6, 17.6 (*C*H$_3$); *m*/*z* (FAB) 394 (MH$^+$, 53%).

(4*R*)-1-[*N*-(1*R*)-1-Phenylethyl]-4-methylazetidin-2-one 8a

β-Lactam **8a** was prepared by the decomplexation of complex **7a** (100 mg, 0.28 mmol) with bromine (90 mg, 0.56 mmol) in accordance with general procedure 3. The crude material was subjected to flash chromatography on silica gel [25% ethyl acetate–petrol; R_f 0.30] to give the title compound as a colourless oil (23 mg, 43%); $[a]_D^{22}$ +64.2 (*c* 0.95, $CHCl_3$) {lit.[7] (enantiomer) $[a]_D^{21}$ −68.9 (*c* 1.61, $CHCl_3$)}; ν_{max}($CHCl_3$)/cm^{-1} 1740s (C=O); δ_H(200 MHz; $CDCl_3$) 7.38–7.22 (5H, m, Ph), 4.93 (1H, q, *J* 7.3, NC*H*(CH$_3$)Ph), 3.53 (1H, ABX system; X part, ddq, *J* 6.0, J_{AX} 6.0, J_{BX} 2.4, CH$_3$C*H*CH$_2$), 3.40–2.43 (2H, ABX system; AB part, J_{AX} 6.0, J_{BX} 2.4, J_{AB} 14.5, CH$_3$CHC*H*$_2$), 1.64 (3H, d, *J* 7.3, NCH(C*H*$_3$)Ph), 1.27 (3H, d, *J* 6.0, C*H*$_3$CHCH$_2$).

(4*S*)-1-[*N*-(1*R*)-1-Phenylethyl]-4-phenylazetidin-2-one 8b

β-Lactam **8b** was prepared by the decomplexation of complex **7b** (126 mg, 0.29 mmol) with bromine (94 mg, 0.59 mmol) in accordance with general procedure 3. The crude material was subjected to flash chromatography on silica gel [25% ethyl acetate–petrol; R_f 0.30] to give the title compound as a colourless oil (30 mg, 41%); $[a]_D^{22}$ −57.6 (*c* 1.03, $CHCl_3$) {lit.[7] (enantiomer) $[a]_D^{21}$ +57.9 (*c* 1.06, $CHCl_3$)}; ν_{max}($CHCl_3$)/cm^{-1} 1747s (C=O); δ_H(200 MHz; $CDCl_3$) 7.34–7.18 (10H, m, Ph), 5.07 (1H, q, *J* 7.2, NC*H*(CH$_3$)Ph), 4.31 (1H, ABX system; X part, dd, J_{AX} 5.3, J_{BX} 2.5, NC*H*CH$_2$), 3.32–2.78 (2H, ABX system; AB part, J_{AX} 5.3, J_{BX} 2.5, J_{AB} 14.7, C*H*$_2$CO), 1.31 (3H, d, *J* 7.2, NCH(C*H*$_3$)Ph).

(4*S*)-1-[*N*-(1*R*)-1-Phenylethyl]-4-(*E*)-propenylazetidin-2-one 8c

A stirred solution of complex **7c** (70 mg, 0.18 mmol) in dichloromethane (2 cm^3) at −78 °C was treated with *N*-bromosuccinimide (63 mg, 0.36 mmol) as a dichloromethane solution. The resulting solution was allowed to warm to ambient temperature over 0.5 h with an attendant colour change from orange to red. The solution was treated with triethylamine (0.15 cm^3, 1.1 mmol) and stirred at ambient temperature for 1 h with subsequent removal of volatiles *in vacuo*. The residue was redissolved in diethyl ether and filtered through a plug of alumina (grade IV). Concentration of the filtrate *in vacuo* afforded the crude material which was subjected to flash chromatography on silica gel [50% ethyl acetate–petrol; R_f 0.25] to give the title compound as a colourless oil (20 mg, 51%); $[a]_D^{22}$ +41.0 (*c* 0.80, $CHCl_3$) {lit.[7] (enantiomer) $[a]_D^{21}$ −39.4 (*c* 1.02, $CHCl_3$)}; ν_{max}($CHCl_3$)/cm^{-1} 1745s (C=O); δ_H(200 MHz; $CDCl_3$) 7.40–7.23 (5H, m, Ph), 5.63 (1H, dq, AB system, *J* 6.3, 14.2, (*E*)-CH$_3$C*H*=CH), 5.46 (1H, m, AB system, *J* <2.0, 8.8, 14.2, (*E*)-CH$_3$C*H*=CH), 4.94 (1H, q, *J* 6.5, PhC*H*(CH$_3$)N), 3.82 (1H, ABX system; X part, ddd, J_{AX} 5.3, J_{BX} 2.4, *J* 8.8, CH=CHC*H*CH$_2$), 3.02, 2.59 (2H, ABX system; AB part, J_{AX} 5.3, J_{BX} 2.4, J_{AB} 14.5, CH=CHCHC*H*$_2$), 1.79 (3H, d, *J* 6.3, C*H*$_3$-CH=CH), 1.56 (3H, d, *J* 6.5, PhCH(CH$_3$)N).

Methyl (2*S*)-2-{(3*S*)-3-[*N*-(1*R*)-1-phenylethyl-*N*-prop-2-enylamino]-3-phenylpropanamido}-3-phenylpropanoate 11

A suspension of L-phenylalanine methyl ester hydrochloride (460 mg, 2.15 mmol) in THF was treated with triethylamine (0.6 cm^3, 4.30 mmol) and stirred at ambient temperature for 1 h. The resulting suspension was filtered and volatiles removed *in vacuo* to give the free amino ester as a colourless oil which was subsequently dissolved in dichloromethane.

The solution was treated with complex **5b** (200 mg, 0.43 mmol, 90% de) as a solution in dichloromethane and the resulting mixture cooled to −42 °C. A dichloromethane solution of *N*-bromosuccinimide (151 mg, 0.86 mmol) was then added to the stirred mixture *via* cannula and the resulting solution allowed to reach ambient temperature over 3 h. The solution was treated with triethylamine (0.30 cm^3, 2.15 mmol) and stirring was continued for 1 h. Volatiles were removed *in vacuo* and the residue dissolved in diethyl ether; subsequent filtration through a plug of alumina (grade IV) followed by concentration of the filtrate *in vacuo* afforded the crude material as a red oil. This oil was dissolved in ethyl acetate and washed with saturated aqueous citric acid (5 × 10 cm^3) and the combined aqueous washings basified with sodium hydroxide pellets. The pH was adjusted to 9–10 and the aqueous extracted with ethyl acetate (2 × 20 cm^3), the combined organic fractions washed with water (2 × 20 cm^3) and finally washed with brine (2 × 20 cm^3). The solution was dried over magnesium sulfate and filtered with subsequent removal of solvent under reduced pressure to afford the crude material as a brown oil. Purification by flash chromatography on silica gel gave the title compound [20% ethyl acetate–petrol; R_f 0.30] as a colourless oil (49 mg, 24%) (Found: C, 76.3; H, 7.4; N, 6.1. $C_{30}H_{35}N_2O_3$ requires C, 76.6; H, 7.3; N, 9.95%); ν_{max}($CHCl_3$)/cm^{-1} 3424m (NH), 1730s (CO_2CH_3), 1661s, 1510m (CONHR); δ_H(500 MHz; $CDCl_3$) 7.40–6.96 (15H, m, Ph), 6.89 (1H, d, *J* 7.0, N*H*), 5.66–5.59 (1H, m, NCH$_2$C*H*=CH$_2$), 5.16–4.99 (2H, m, NCH$_2$CH=C*H*$_2$), 4.77 (1H, ABX system; X part, dt, J_{AX} 6.4, J_{BX} 6.4, *J* 7.0, PhCH$_2$-C*H*(NHCOR)CO$_2$CH$_3$), 4.40 (1H, ABX system; X part, dd, J_{AX} 7.2, J_{BX} 7.2, C*H*$_2$CHPh), 4.08 (1H, q, *J* 6.8, PhC*H*-(CH$_3$)N), 3.66 (3H, s, CO$_2$C*H*$_3$), 3.25, 3.14 (2H, ABX system; AB part, J_{AX} 7.0, J_{BX} 5.5, J_{AB} 15.0, NC*H*$_2$CH=CH$_2$), 3.07, 2.97 (2H, ABX system; AB part, J_{AX} 6.4, J_{BX} 6.4, J_{AB} 13.8, PhC*H*$_2$-C*H*(NHCOR)CO$_2$CH$_3$), 2.93, 2.52 (2H, ABX system; AB part, J_{AX} 7.2, J_{BX} 7.2, J_{AB} 15.5, C*H*$_2$CHPh), 1.11 (3H, d, *J* 6.8, CH$_3$); δ_C(125 MHz; $CDCl_3$) 172.3, 171.5 (*C*=O), 144.8, 141.0, 136.5 (Ph: C$_{ipso}$), 138.5 (NCH$_2$*C*H=CH$_2$), 129.6, 128.9, 128.8, 128.7, 128.4, 128.1 (Ph: C$_{ortho/meta}$), 127.8, 127.4, 127.2 (Ph: C$_{para}$), 116.9 ((NCH$_2$CH=*C*H$_2$), 59.1, 56.8 (N*C*H), 53.8 (CO$_2$*C*H$_3$), 52.5 (N*C*HCO$_2$CH$_3$), 50.1 (N*C*H$_2$CH=CH$_2$), 39.8, 38.3 (*C*H$_2$CO/PhCH$_2$), 16.7 (PhCH(*C*H$_3$)N); *m*/*z* (CI) 471 (MH$^+$, 100%).

***tert*-Butyl (2*S*)-2-{(3*S*)-3-[*N*-(1*R*)-1-phenylethyl-*N*-prop-2-enylamino]-3-phenylpropanamido}propanoate 12**

A suspension of L-alanine *tert*-butyl ester hydrochloride (232 mg, 1.29 mmol) in THF was treated with triethylamine (0.6 cm^3, 4.30 mmol) and stirred at ambient temperature for 1 h. The resulting suspension was filtered and volatiles removed *in vacuo* to give the free amino ester as a colourless oil. The oil was treated with complex **5b** (200 mg, 0.43 mmol, 90% de) as a solution in dichloromethane and the resulting mixture cooled to −42 °C. A dichloromethane solution of *N*-bromosuccinimide (151 mg, 0.86 mmol) was added to the stirred mixture *via*

cannula and the mixture allowed to reach ambient temperature over 3 h. The solution was treated with triethylamine (0.30 cm^3, 2.15 mmol) and stirring was continued for 1 h. Volatiles were removed *in vacuo* and the residue dissolved in diethyl ether, subsequent filtration through a plug of alumina (grade IV) followed by concentration of the filtrate *in vacuo* afforded the crude material as a red oil. This oil was dissolved in ethyl acetate and washed with saturated aqueous citric acid (5 × 10 cm^3) and the combined aqueous washings basified with sodium hydroxide pellets. The pH was adjusted to 9–10 and the aqueous washings extracted with ethyl acetate (2 × 20 cm^3) and the combined organic fractions washed with water (2 × 20 cm^3) and finally with brine (2 × 20 cm^3). The solution was dried over magnesium sulfate and filtered with subsequent removal of solvent under reduced pressure to afford the crude material as a brown oil. Purification by flash chromatography on silica gel gave the title compound [20% ethyl acetate–petrol; R_f 0.35] as a colourless oil (37 mg, 20%) (Found: C, 74.4; H, 8.1; N, 6.2. $C_{27}H_{36}N_2O_3$ requires C, 74.3; H, 8.3; N, 6.4%); $\nu_{max}(CHCl_3)$/cm^{-1} 3427m (NH), 1742s (CO_2CH_3), 1662s, 1510m (CONHR); δ_H(200 MHz; $CDCl_3$) 7.44–7.18 (10H, m, Ph), 6.90 (1H, d, *J* 6.8, N*H*), 5.98–5.77 (1H, m, $NCH_2CH{=}CH_2$), 5.21–5.04 (2H, m, $NCH_2CH{=}CH_2$), 4.47 (1H, ABX system; X part, dd, J_{AX} 8.6, J_{BX} 6.0, CH_2CHPh), 4.37 (1H, dq, *J* 6.8, 7.2, CH_3CHNH), 4.10 (1H, q, *J* 6.9, $PhCH(CH_3)N$), 3.39–3.12 (2H, m, $NCH_2CH{=}CH_2$), 3.05–2.41 (2H, ABX system; AB part, J_{AX} 8.6, J_{BX} 6.0, J_{AB} 15.2, CH_2CHPh), 1.46 (9H, s, $C(CH_3)_3$), 1.25 (3H, d, *J* 7.2, $CH_3CHCO_2C(CH_3)_3$), 1.11 (3H, d, *J* 6.9, $PhCH(CH_3)N$); δ_C(125 MHz; $CDCl_3$) 172.1, 170.8 (*C*=O), 144.6, 141.0 (Ph: C_{ipso}), 138.3 ($NCH_2CH{=}CH_2$), 128.4, 128.2, 128.0, 127.7 (Ph: $C_{ortho/meta}$), 127.3, 126.7 (Ph: C_{para}), 116.4 ($NCH_2CH{=}CH_2$), 81.6 ($C(CH_3)_3$), 59.0, 56.4 (*C*HN), 49.8 ($NCH_2CH{=}CH_2$), 48.6 ($NCHCO_2C(CH_3)_3$), 40.0 ($COCH_2$), 27.9 ($C(CH_3)_3$), 18.6, 16.1 (CH_3); *m*/*z* (CI) 437 (MH^+, 100%).

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