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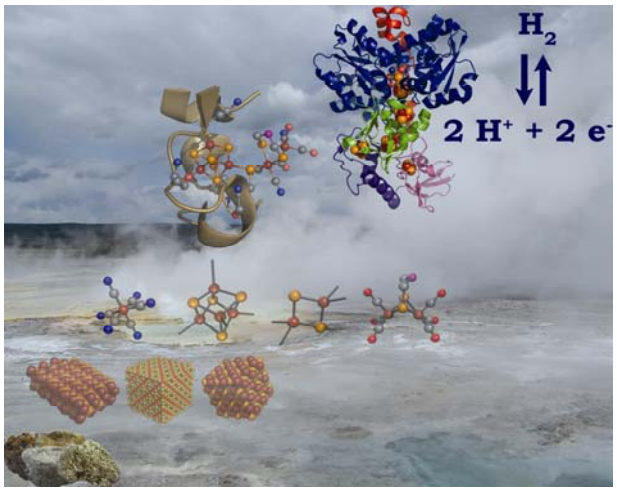

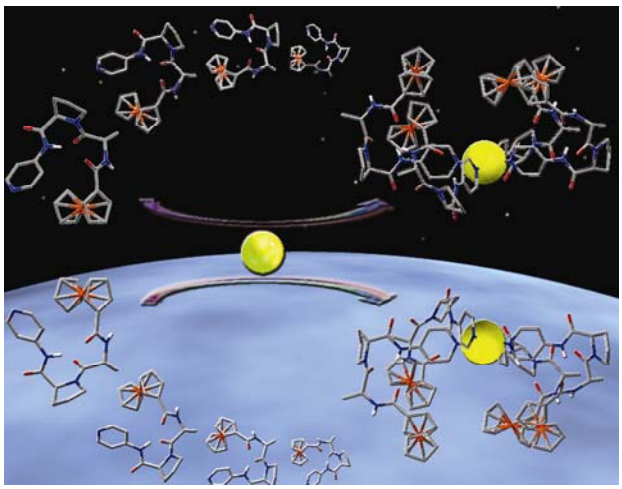

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Synthesis and characterisation of hetero-bimetallic organometallic phenylalanine and PNA monomer derivatives†

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The rational, sequential synthesis of two hetero-bimetallic derivatives of the amino acid phenylalanine and one thymine (T) peptide nucleic acid (PNA) monomer is reported. Ferrocene carboxylic acid and (η-ethene)bis(triphenylphosphine)platinum(0) were successfully reacted with propargylamide amino acid (**1a** and **1b**) or a T PNA monomer derivative (**6**) to give the expected three bimetallic compounds **4a**, **4b** and **9** in good yield. An enzymatic route using cross-linked enzyme crystals (CLEC) of subtilopeptidase A in organic solvents gave the ferrocene carboxylate phenylalanine propargylamide precursor (Fc-CO-Phe-NH-CH_2-CCH, **3a**) in comparable yield and purity to the traditional deprotection-peptide coupling sequence. ^{31}P NMR spectra of these bioorganometallics showed two doublets with ^{195}Pt satellites corresponding to two chemically different ^{31}P atoms. Interestingly, in the case of the T PNA monomer derivative **9**, these signals were also doubled in a 60 : 40 ratio as a consequence of the existence of two slowly interconverting isomers in solution. Furthermore, the single-crystal X-ray structures of **3a** and the hetero-bimetallic phenylalanine derivative **4b** were determined, showing the presence of the two organometallics moieties separated by *ca.* 8.5 Å in **4b** as well as illustrating the stability of such compounds.

Introduction

For a long time, organometallics have been neglected for the labelling of biomolecules, mainly because they were thought to be too unstable in an aqueous, aerobic environment. Recently, however, numerous examples of the labelling of DNA, peptide nucleic acids (PNAs), peptides, hormones, drugs and proteins to organometallic compounds have been reported for different applications including biosensing, cytotoxicity, cellular localisation or increase of cellular uptake.[1–8] Thus, low-valent, organometallic fragments are obviously well-suited for a selective labelling of biomolecules. In the great majority of cases, the conjugates contain one organometallic complex per biomolecule, in most cases ferrocene.[9,10] An unspecific labelling with an ill-defined number of metal complexes was observed for reactions with proteins, such as glucose oxidase (GOD).[11–15]

There are, however, to the best of our knowledge, no reports on the rational, well-designed synthesis of hetero-multiorganometallic-containing biomolecules, such as peptides, DNA or PNA.[16] This is regrettable as it would be very interesting to combine the properties of several different organometallics into the same biomolecule. There are, however, a few reports on biomolecules containing different coordination complexes. For example, heterobimetallic amino acid derivatives were synthesised by Beck and co-workers[8,17] for peptidomimetic purposes. Barton's group synthesised DNA oligomers with covalently attached rhodium and ruthenium complexes for the study of electron transfer through DNA.[18] For similar endeavours, Ogawa *et al.* studied the electron transfer along artificial β-strands between cobalt and ruthenium complexes.[19]

However, all the bimetallic biomolecules described above contain at least one classical coordination complex with an (N,O) ligand bound to a metal ion. Interestingly, Lang and co-workers recently reported the synthesis, characterisation and electrochemical studies of up to heteropenta-organometallics.[20] However, the bridging units between the metal complexes were not biomolecules. The reason for this lack of bioorganometallic compounds with several different metals is possibly the difficulty to identify suitable chemistry. Any metal-containing compound that could be considered as a promising candidate must itself be stable in aerobic, aqueous solutions. Moreover, the chemistry of attaching the metal complex to the biomolecule must be "bio-compatible" with the variety of functional groups present in the biomolecule, and yet specific for a given site of attachment.

In this contribution, we report our initial results on the rational, sequential formation of hetero-bimetallic derivatives of the amino acid phenylalanine and their crystallographic characterisation. Using the same chemistry, the synthesis of a hetero-bimetallic thymine (T) PNA monomer is also described, using ferrocene and bis(phosphine)platinum–alkyne complexes.

Results and discussion

The synthetic strategy chosen to achieve our primary aim, namely the synthesis of hetero-bimetallic amino acid or PNA monomer derivatives, was to attach a carboxylic acid metal derivative to their *N*-termini and an alkyne group to their *C*-termini. The

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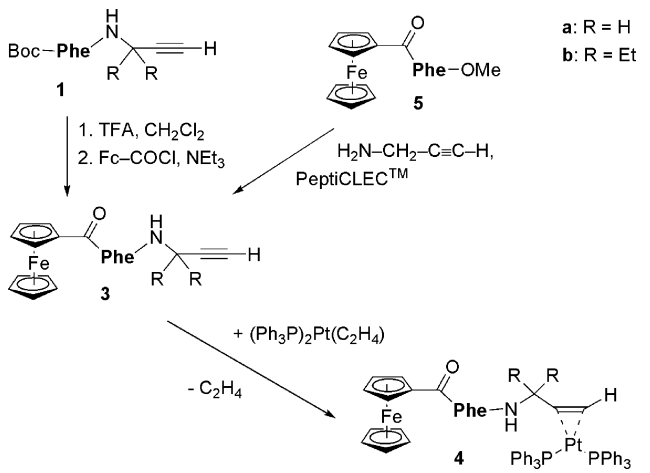
† CCDC reference numbers 702132 (**3a**) and 702132 (**4b**). For crystallographic data in CIF or other electronic format see DOI: 10.1039/b819169g

latter would then serve as a ligand for another organometallic compound. Because of its favourable electrochemical properties and chemical robustness, ferrocene carboxylic acid was chosen as the first organometallic moiety.[9,21] Also, importantly for the scope of this research, propargylamine derivatives of amino acids were already used in Sonogashira coupling to suitably functionalised organometallics by our group.[22,23] In these reactions, the alkyne group was found to be unreactive under conditions typically employed in peptide chemistry such as deprotection and coupling to activated amino acids. A further significant example of the suitability of the alkyne group in biomolecules is the success of the so-called "click chemistry".[24–28] Alkynes and azido derivatives proved to be very stable and unreactive in biomolecules unless heated or in the presence of a Cu(I) catalyst,[29] or if activated alkynes[30–33] or oxanobornadiene derivatives[34,35] are used.

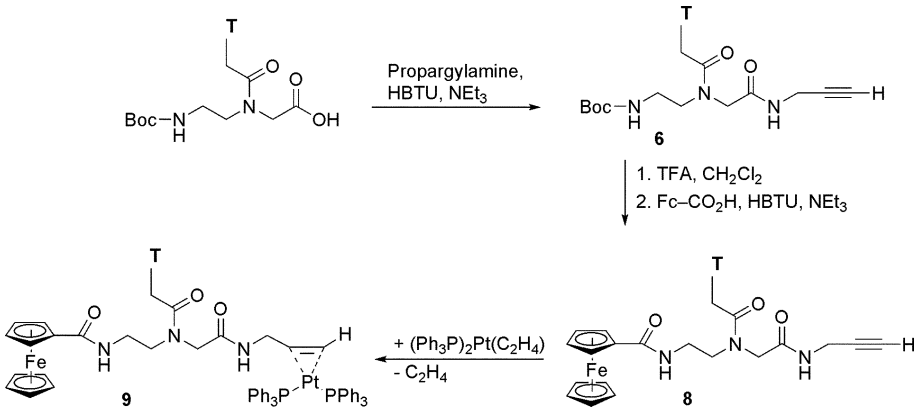
To achieve the preparation of both amino acid and PNA monomer heterobimetallics, propargylamine was first reacted with the *C*-terminus of the amino acid or the PNA monomer using standard peptide coupling. A ferrocene moiety was then introduced to the *N*-terminus. Finally, a Pt(0) organometallics, namely (η-ethene)bis(triphenylphosphine)platinum(0) [$(C_2H_4)Pt(Ph_3P)_2$],[36] was reacted stoichiometrically with the alkyne containing amino acid or PNA monomer (Scheme 1 and 2), as it readily reacts with alkynes to form stable metal complexes, with the release of ethene.[37–39]



Scheme 1 Synthesis of **4**.

In the case of the heterobimetallic amino acid derivatives, the synthesis of a suitable ferrocene derivative was accomplished by two different routes. First, *N*-Boc-protected propargylamine derivatives of phenylalanine (**1**) [22,40] were Boc-deprotected by TFA (Scheme 1, **a**: R = H for propargylamine; **b**: R = Et for 1,1-diethylpropargylamine). Without isolation, the intermediate phenylalaninylpropargylamides **2** were reacted with ferrocene carboxylic acid chloride[41] to yield **3** in >80% yield. **3a** could also be obtained by an enzymatic route starting from ferrocene phenylalanine methyl ester **5**.[42,43] Although the methyl ester is most difficult to remove chemically, it proved to be the best choice for the direct enzymatic transformation with propargylamine to **3a**. This reaction was catalyzed by CLEC-immobilized subtilopeptidase A at 37 °C in acetonitrile. The reaction was monitored by HPLC and stopped after 80 h when maximum transformation was achieved (80% of **3a**). A number of enzymatic transformations have been performed on organometallic compounds but they generally demand aqueous solvents.[44,45] CLEC,[46–49] on the contrary, are designed to work in organic solvents and are therefore much better suited for applications in organometallic chemistry. For work-up, the catalyst is simply removed by filtration and the product is purified by preparative HPLC. The overall yield of **3a** is similar for both preparations. In addition, the CLEC catalyst can be re-used without notable loss of activity.

Compounds **3** were reacted with (η-ethene)bis(triphenylphosphine)platinum(0) to yield the heterobimetallic compounds **4**. The reaction is quantitative with elimination of ethene and **4a** (R = H) and **4b** (R = Et) are obtained practically pure after removal of all volatiles from the reaction mixture. The formation of **4** from **3** is indicated by a number of characteristic spectroscopic changes. In $CDCl_3$, the alkyne proton of **3b** is observed as a singlet at 2.31 ppm in the ^{1}H NMR spectrum. On the contrary, in **3a**, a triplet with $^4J_{HH} = 2.3$ Hz is observed at 2.17 ppm due to good coupling transmission through the triple bond. After coordination of the Pt(0) fragment to the alkyne, this signal shifts to 6.46 ppm and now appears as a doublet of doublets due to coupling to the two chemically inequivalent ^{31}P nuclei (**4a**: $^3J_{PH} = 20$ Hz and $^3J_{P'H} = 11$ Hz). In addition, Pt-satellites of this signal indicate coupling to ^{195}Pt ($^2J_{PtH} = 55$ Hz in **4a**). The ^{31}P NMR spectrum of **4** (see Fig. 3 for **4a**) clearly shows two doublets with different



Scheme 2 Synthesis of **9**.

$^1J_{PtP}$ coupling of about 3550 Hz for two inequivalent phosphorus atoms as expected for a square planar coordination around the Pt centre. All these NMR parameters correlate well with what was found for other organoplatinum compounds.[50–52] Finally, a strong band is observed at 2123 and 2110 cm^{-1} in the Raman spectrum for **3a** and **3b**, respectively, assigned to the terminal alkyne, which disappeared in **4**. Importantly, the bimetallic compounds **4** are air-stable in the solid state and in solution and can be handled without special precautions.

Single crystals of **3a** and **4b** were grown from $CHCl_3$ and diethyl ether–pentane, respectively. Fig. 1 shows an ORTEP plot for compound **3a**, together with selected bond lengths and angles. The unit cell of **4b** contains two independent molecules, the geometries of which are very similar. An ORTEP plot of molecule A is shown in Fig. 2 together with selected bond lengths and angles, and in the following only pertinent structural features of molecule A are discussed. All amide bonds are *trans*-configured and practically planar. The ferrocene groups are almost eclipsed (3.6° dihedral twist angle for **3a**, 11.0° for **4b**). The C≡C triple bond is elongated by 0.10 Å upon Pt coordination and the alkyne group is no longer linear as indicated by a C–C≡C angle of 141.8° in **4b**. The Pt atom in **4b** is square-planar coordinated by two phosphorus atoms and the alkyne carbon atoms. The structural parameters of the Pt-alkyne group resemble those of the $(PPh_3)_2Pt$(tolane)[37] or $(PPh_3)_2Pt(C_2(CF_3)_2)$[53] complexes. The bonding situation in alkyne-Pt(0) complexes has been the subject of theoretical studies.[54] In **4b**, the distance between the two metal centres is 8.7 Å. Inter-residue hydrogen bonds are crucial for the formation and stability of secondary and tertiary structures in peptides. They also govern the packing of **3a** and **4b** in the solid state. In **3a**, the chiral information of each single molecule is transformed in the chiral space group $P3_121$ in a fascinating way: each molecule of **3a** has two amide bonds that can be used for intermolecular hydrogen bonds. Two neighbouring molecules form a couple with two hydrogen bonds by using one of their two amide groups. The second amide bond forms hydrogen bridges to the neighbouring couple, thus leading to a one-dimensional supramolecular "sheet" perpendicular to the crystallographic *c*-axis. **4b** also forms extended networks *via* hydrogen bridges in the solid state, but the packing in the unit cell

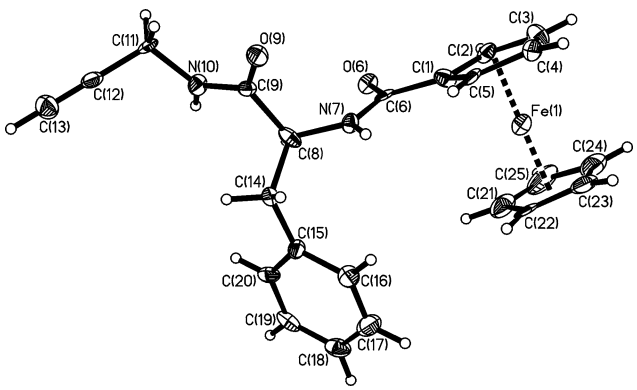


Fig. 1 ORTEP plot (40% probability) of **3a** with numbering scheme. Selected bond lengths and angles: Fe–C_{Cp} (av.) 2.047 and 2.039 Å (unsubstituted Cp), Fe–Cp(centroid) 1.656 and 1.643 Å (unsubstituted Cp), C(1)–C(6) 1.514(10) Å; Cp(centroid)–Fe–Cp(centroid) 177.5°, C(1)–C(6)–N(7) 117.3(6)°, angle between planes C(2)–C(1)–C(5) and O(6)–C(6)–N(7) 10.8°; angle between Cp planes 2.4°.

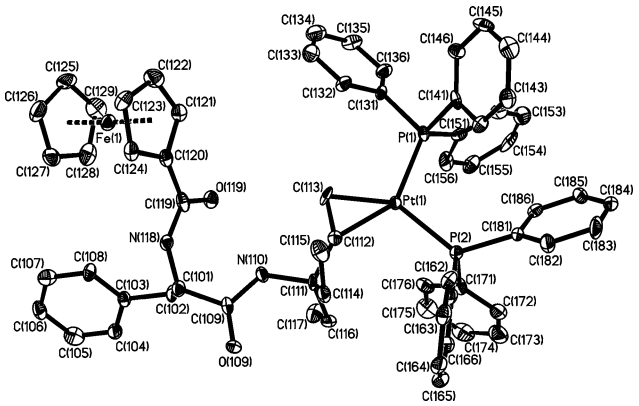


Fig. 2 ORTEP plot (50% probability) of **4b** (molecule A) with numbering scheme. Pertinent parameters for molecule B differ only marginally from those given here. Hydrogen atoms are omitted for clarity. Selected bond lengths and angles: Pt(1)–C(112) 2.053(10) Å, Pt(1)–C(113) 2.034(10) Å, Pt(1)–P(1) 2.270(2) Å, Pt(1)–P(2) 2.292(3) Å, C(112)–C(113) 1.279(13) Å, Fe–C_{Cp} (av.) 2.050 and 2.048 Å (unsubstituted Cp), Fe–Cp(centroid) 1.652 and 1.649 Å (unsubstituted Cp), C(119)–C(120) 1.473(15) Å; P(1)–Pt(1)–P(2) 107.3(1)°, C(111)–C(112)–C(113) 141.9(10)°, Cp(centroid)–Fe–Cp(centroid) 177.1°, C(120)–C(119)–N(118) 117.4(9)°, angle between planes C(120)–C(124) and O(119)–C(119)–N(118) 1.6°; angle between Cp planes 3.3°.

appears to be mainly governed by the need to accommodate the bulky triphenylphosphine groups.

For the synthesis of the hetero-bimetallic PNA monomer, *N*-Boc-protected thymine PNA monomer (Boc-T-PNA-OH) was turned into the propargylamide **6** in 90% yield. The *N*-terminus of **6** was Boc-deprotected with TFA in CH_2Cl_2 to give **7**, which was then reacted with ferrocene carboxylic acid in the presence of the coupling reagent HBTU to yield the ferrocene derivative **8**. The ferrocene-T-PNA-propargylamide **8** was isolated and fully characterised. The spectroscopic data of **8** resemble those of the ferrocene T-PNA methyl ester Fc-T-PNA-OMe.[55] In NMR spectroscopy, because of *cis–trans* isomerism about the central amide bond, all signals are doubled in a 60 : 40 ratio which are in slow exchange on the NMR time scale (400 MHz at room temperature). The solvent dependence of the ratio of the two species, denoted major (ma) and minor (mi), is well established and the barrier of rotation about the central amide bond has been determined to be about 60 kJ mol^{-1}.[56–58] In **8**, additional characteristic signals for the alkyne group are observed at 2.45 ppm (ma) and 2.47 (mi) in the ^{1}H NMR spectrum with characteristic $^4J_{HH}$ coupling as observed for **3a**. **8** reacts smoothly with (η-ethene)bis(triphenylphosphine)platinum(0) to yield the bimetallic PNA derivatives **9** in almost quantitative yield. Similar to compounds **4**, Pt coordination to the alkyne group is immediately established from the ^{1}H NMR spectrum of **9** by the disappearance of the alkyne signal at 2.45 ppm and the appearance of a new signal at 6.5 ppm with ^{31}P coupling and ^{195}Pt satellites. The ^{31}P NMR spectrum of **9** is most instructive (Fig. 3). As for **4b**, there are two doublets with ^{195}Pt satellites for two chemically different ^{31}P atoms. However, these signals are also doubled as a consequence of the existence of two slowly interconverting isomers in solution. The major/minor ratio of 60 : 40 in the ^{31}P NMR spectrum fits perfectly with the value of 62 : 38 determined in the ^{1}H NMR spectrum of **9**, given the limited accuracy of the

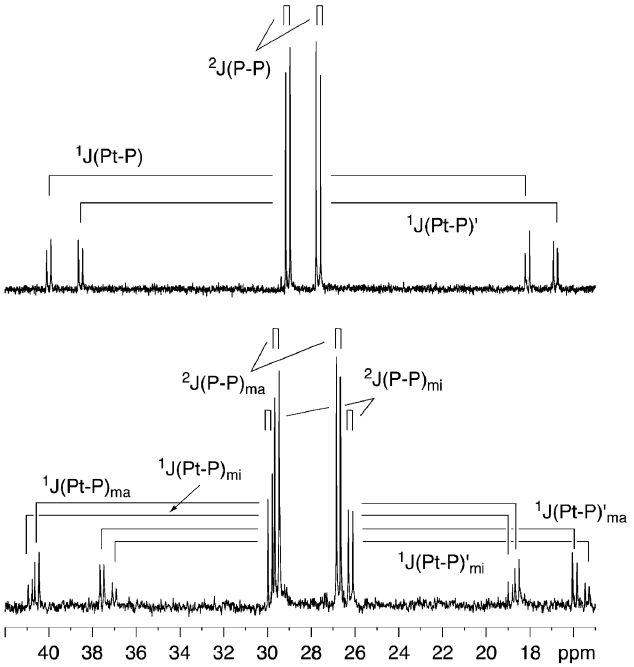


Fig. 3 ^{31}P NMR spectra of **4a** (top) and **9** (bottom). Due to the existence of two isomers in solution, denoted major (ma) and minor (mi), all signals are doubled in a 60 : 40 ratio in the bottom spectrum (see text).

integration (overlapping signals in the ^{1}H NMR spectrum and poor S/N ration of the ^{31}P NMR spectrum). We were unable to grow crystals of **9** of suitable quality for an X-ray structure determination. Indeed, *no* crystal structure of *any* PNA monomer has been reported to date to the best of our knowledge and this may possibly be a consequence of the *cis–trans* flexibility of PNA monomers. However, the spectroscopic data and in particular a comparison of the ^{31}P NMR spectra presented in Fig. 3 support the suggested constitution of **9** unambiguously.

Conclusions

In this work, to the best of our knowledge, the first hetero-organobimetallic amino acid (**4a** and **4b**) and PNA (**9**) derivatives are reported. They contain a ferrocene group attached to their *N*-termini and a bis(triphenylphosphine)platinum(0) moiety complexed to an alkyne bond at their *C*-termini. The ferrocenoyl phenylalanine propargylamide **3a** could be obtained by a classical deprotection-peptide coupling reaction or an enzymatic reaction using a CLEC peptidase in organic solvents. While both reactions yield **3a** in similar yield and purity, the CLEC reaction is easier to perform experimentally but required HPLC purification of the product. All compounds were fully characterised spectroscopically. Hence, the complexation of the alkyne derivatives **3a**, **3b** and **8** with bis(triphenylphosphine)platinum(0) was confirmed by Raman spectroscopy with the disappearance of the alkyne band at about 2100 cm^{-1}. Furthermore, ^{31}P NMR spectra of **4a** and **4b** contain two doublets with ^{195}Pt satellites corresponding to two chemically different ^{31}P atoms. For **9**, these signals are doubled as a consequence of the existence of two slowly interconverting isomers in solution. For compounds **3a** and **4b**, the solid-state structures could be determined by single-crystal X-ray crystallography. In conclusion, amino acid derivatives and a thymine PNA monomer were used to exemplify a general principle for the chemoselective introduction of two different organometallic groups into biomolecules by using chemically selective reactions at two different sites of a biomolecule. Transfer of this chemistry to larger biomolecules including peptides and PNA oligomers is currently in progress in our laboratory.

Experimental

Materials

All reactions were carried out in ordinary glassware and solvents were used without further precautions except where indicated. Chemicals were purchased from commercials suppliers and used as received. Only enantiomerically pure L-phenylalanine was used. PeptiCLEC™ catalyst was purchased from Altus Biologics Inc. Cambridge, Massachusetts, USA. The *N*-Boc-protected T-PNA monomer was purchased from PE Applied Biosystems GmbH, Weiterstadt, Germany (now available from Link Technologies, Lanarkshire, Scotland or ASM Research Chemicals, Hannover, Germany).

Instrumentation and methods

Elemental analyses were carried out by H. Kolbe, Analytisches Laboratorium, Mülheim on an Analytic Jena multi EA 3100. IR spectra were recorded on a Perkin Elmer System 2000 instrument as KBr disks, additionally in CH_2Cl_2 solution if indicated. Wavenumbers ν are given in cm^{-1}. UV/Vis spectra were recorded on a Perkin Elmer Lambda 19 spectrometer, only the wavelength of the lowest-energy ferrocene transition is given in nm, ε (dm^3 mol^{-1} cm^{-1}) in parentheses. Melting points (uncorrected) were determined on a Tottoli apparatus (Büchi, Switzerland). Mass spectra were recorded by the mass spectrometry service group, Mülheim, on a MAT 8200 (Finnigan GmbH, Bremen) instrument (EI, 70 eV) or on a MAT95 (Finnigan GmbH, Bremen) instrument (ESI, CH_3OH solution, positive ion detection mode). Only characteristic fragments are given with intensities (%) and possible composition in parentheses. Analytical RP-HPLC was carried out on a Nucleosil-N-7-C_{18} column (Nr. 312014, Size 250 × 20 mm) with a Merck C 6200 pump and a Shimadzu SPD-6-A V-detector at 260 and 420 nm. The eluents were a mixture of methanol–water in different ratio. The flow rate was 1 mL min^{-1} (analytical) or 4 mL min^{-1} (preparative). NMR spectra were recorded at room temperature using a Bruker ARX 250 (^{1}H at 250.13 MHz and ^{13}C) or a DRX 400 (^{1}H at 400.13 MHz, ^{13}C and 2D spectra) or DRX 500 (^{1}H at 500.13 MHz, ^{13}C, ^{15}N, 2D) spectrometer. ^{1}H and ^{13}C spectra were referenced to TMS, using the ^{13}C signals or the residual proton signals of the deuterated solvents as internal standards. Positive chemical shift values δ (in ppm) indicate a downfield shift from the standard, only the absolute values of coupling constants are given in Hz. ^{15}N spectra were referenced to the absolute frequency of 50.6969910 MHz, which was the resonance frequency of neat nitromethane under the same experimental conditions. All resonances were assigned by 2D NMR (H–H-COSY and ^{1}H–^{13}C-HMQC for ^{1}J and long-range couplings). Where unambiguous or proven spectroscopically, the following conventions are used: δ/δ' denotes pairs of signals originating from *cis*/*trans* isomers.

^{15}N chemical shifts and coupling constants were taken from the F1 projection of indirect detection ^{1}H–^{15}N correlated 2D spectra with 1024/256 data points in F1/F2, processed after applying a matched cosine function and zero filling in both dimensions.

Synthesis and characterisation

***N*-Boc-protected propargylamine derivative of phenylalanine (1a).** **1a** was prepared following the procedure published by Curran *et al.* The spectroscopic data of the products matched that reported previously.[40]

***N*-Boc-protected propargylamine derivative of phenylalanine (1b).** **1b** was prepared following the procedure published by Metzler-Nolte *et al.*[22] The spectroscopic data of the products matched that reported previously.[22]

General procedure for the synthesis of ferrocene-propargylamine derivatives of phenylanine (3a and 3b). **1a** or **1b**, respectively (5 mmol) were stirred in a mixture of TFA–CH_2Cl_2 (10 mL–20 mL) for 30 min at 0 °C. The volatiles were then evaporated to dryness to give a residual oil. To this residue was then added diethyl ether (40 mL) and a white solid precipitated after stirring for 5 min. The precipitate was filtered off and air-dried to give **2a** or **2b** respectively, which were used for the next synthetic step without further purification.

2a or **2b** (5 mmol), were dissolved in dry THF and then neutralised with NEt_3 (0.51 g, 5 mmol). To this solution were added ferrocene carboxylic acid chloride[41] (1.15 g, 5 mmol) dissolved in dry THF and NEt_3 (0.51 g, 5 mmol). The reaction mixture was stirred for 4 h at room temperature before being filtered. The filtrate was evaporated to dryness. To the residue was then added a mixture of chloroform/water and the phases separated. The organic phase was then washed with H_2O (3×), dried over Na_2SO_4, filtered and then evaporated to dryness to give **3a** and **3b**, respectively (1.82 g, 88% for **3a**; 2.02 g, 86% for **3b**). **3a** can be recrystallised from ethyl acetate–heptane or from chloroform.

Alternative method for the synthesis of 3a through an enzymatic pathway with PeptiCLEC™. **5** (200 mg, 0.51 mmol) was dissolved in acetonitrile. To this solution was added propargylamine (120 mg, 2.04 mmol) and then PeptiCLECL™ (30 mg). This solution was then shaken at 37 °C and the reaction followed by analytical HPLC. After 118 h, the reaction was completed. The product was filtered and then purified by preparative HPLC to give **3a** (170 mg, 80%).

Characterisation data for 3a. Found: C, 66.6; H, 5.4; N, 6.8. Calc. for $C_{23}H_{22}N_2O_2Fe$: C, 66.7; H, 5.4; N, 6.8%. Major IR bands: 3440 (w), 3304 (m), 1665 (m), 1626 (s). Raman: 2123. Mp 184 °C. ^{1}H NMR ($CDCl_3$): 7.31 (1H, m, H_{Phe}), 6.50 (1H, s br, NH_{prop}), 6.20 (1H, d, J = 7.5 Hz, C$_\alpha H$), 4.64 (1H, s, H_{Cp}), 4.54 (1H, s, H_{Cp}), 4.32 (2H, s, H_{Cp}), 4.04 (5H, s, H_{Cp}), 3.98 (2H, m, C≡C–CH_2), 3.16 (2H, m, C$_\beta H_2$), 2.17 (1H, t, J = 2.4 Hz, C≡CH). ^{13}C NMR ($CDCl_3$): 171.3 (*C*O), 171.0 (Fc–*C*O), 136.9, 129.2 128.7, 127.1 (C_{Phe}), 79.2 (C≡*C*H), 74.8 (C_{Cp}), 71.6 (C≡*C*H), 70.7, 69.8, 68.7, 67.8 (*C*H$_{Cp}$), 54.2 (C_α), 37.8 (C_β), 29.0 (C≡CH–*C*H$_2$). ^{15}N NMR ($CDCl_3$): –269 (*N*H$_{Prop}$), –267 (*N*H$_{Phe}$). MS: *m*/*z* 414 (100), 331 (18), 213 (56), 129 (21%).

Characterisation data for 3b. Found: C, 68.8; H, 6.6; N, 5.8. Calc. for $C_{27}H_{32}N_2O_2Fe$: C, 68.9; H, 6.4; N, 6.0%. Major IR bands: 3422 (w), 3304 (br, m), 1665 (m), 1626 (s). Raman: 2110. Mp 184–187 °C. ^{1}H NMR ($CDCl_3$): 7.32–7.22 (5H, m, H_{Phe}), 6.34 (1H, d, NH_{Phe}), 6.17 (1H, s, N$_{DEPA}H$), 4.72 (1H, m, C$_\alpha H$), 4.64 (1H, s, H_{Cp}), 4.56 (1H, s, H_{Cp}), 4.30 (2H, s, H_{Cp}), 4.04 (5H, s, H_{Cp}), 3.13 (2H, m, C$_\beta H_2$), 2.31 (1H, s, C≡CH), 2.01–1.92 (2H, m, CH_2CH$_3$), 1.85–1.72 (2H, m, CH_2CH$_3$), 0.90–0.83 (6H, m, CH$_2$CH_3). ^{13}C NMR ($CDCl_3$): 170.7 (*C*O), 170.0 (Fc–*C*O), 136.9, 129.3 128.8, 127.1 (C_{Phe}), 84.6 (C≡*C*H), 75.0 (C_{Cp}), 71.6 (C≡*C*H), 70.6, 69.8, 68.5, 67.9 (*C*H$_{Cp}$), 56.6 (*C*(Et)$_2$), 54.8 (C_α), 38.1 (C_β), 30.4 (*C*H$_2$CH$_3$), 8.39 and 8.43 (CH$_2$*C*H$_3$). ^{15}N NMR ($CDCl_3$): –255 (*N*H$_{DEPA}$), –266 (*N*H$_{Phe}$). MS: *m*/*z* 470 (100), 331 (14), 213 (60), 185 (24), 129 (22%).

General procedure for the synthesis of ferrocene–Pt(0)–propargylamine derivatives of phenylalanine (4a and 5a). A solution of $(C_2H_4)Pt(PPh_3)_2$ (0.37 g, 0.50 mmol) in degassed THF (30 mL) was added dropwise, under Ar, to a solution of the alkyne **3a** or **3b** (0.50 mmol) in degassed THF (40 mL). After evolution of gas had ceased, stirring was continued for an additional hour at room temperature and all volatiles were removed from the reaction mixture *in vacuo*. Dry and degassed diethyl ether (20 mL) was then added to the residue, which was filtered through a cannula. The solution was evaporated to dryness to give the pure compound **4a** or **4b**, respectively (550 mg, 97% for **4a** and 530 mg, 89% for **4b**).

Characterisation data for 4a. Found: C, 62.3; H, 4.6; N, 2.4. Calc. for $C_{59}H_{52}N_2O_2FePtP_2$: C, 62.5; H, 4.6; N, 2.5%. Major IR bands: 3423 (br, m), 3293 (s), 1655 (s), 1648 (s), 1625 (s). Mp 118 °C (decomp.). ^{1}H NMR ($CDCl_3$): 7.31–7.09 (35H, m, H_{Phe} and H_{PPh_3}), 6.47–6.36 (1H, dd, CH), 6.25 (1H, d, J = 8.0 Hz, NH_{Phe}), 5.72 (1H, br, NH_{Prop}), 4.61 (1H, m, H_{Cp}), 4.51 (1H, s, H_{Cp}), 4.41 (1H, m, C$_\alpha H$), 4.28 (2H, s, H_{Cp}), 4.10 (2H, m, CH_2), 4.05 (5H, s, H_{Cp}), 2.90 (2H, m, C$_\beta H_2$). ^{13}C NMR ($CDCl_3$): 169.9 and 169.87 (*C*O), 136.7, 129.3 128.7, 126.6 (C_{Phe}), 136.9–136.8 (6C, C_{ipso}), 134.0–133.7 (12C, C_{ortho}), 129.3–129.1 (6C, C_{para}), 128.0–127.9 (12C, C_{meta}), 125.2 (HC≡*C*(Pt)), 108.5 (H*C*≡C(Pt)), 75.6, 70.4, 69.8, 68.6, 67.7 (C_{Cp}), 53.9 (C_α), 38.6 (C$_\beta$), 37.7 and 37.6 (*C*H$_2$). ^{31}P NMR ($CDCl_3$): 2 doublets at 29.1 and 27.7 ppm ($^{2}J_{P1–P2}$ = 31 Hz, $^{1}J_{Pt–P1}$ = 3545 Hz, $^{1}J_{Pt–P2}$ = 3550 Hz). ^{15}N NMR ($CDCl_3$): –267 (*N*H$_{Phe}$), –257 (*N*H$_{Prop}$). ESI-MS (positive, CH_2Cl_2): *m*/*z* 1134 [M + H]$^+$, 1134 [M + Na]$^+$.

Characterisation data for 4b. Found: C, 63.7; H, 5.1; N, 2.4. Calc. for $C_{63}H_{60}N_2O_2FePtP_2$: C, 63.6; H, 5.1; N, 2.4%. Major IR bands: 3437 (br, m), 3289 (br, m), 1655 (m), 1644 (m), 1630 (m). Mp 112 °C (decomp.). ^{1}H NMR ($CDCl_3$): 7.40–7.00 (35H, m, H_{Phe} and H_{PPh_3}), 6.26 (1H, d, NH_{Phe}, J = 5 Hz), 6.15–5.95 (1H, dd, CH), 5.78 (1H, s, br, N$_{DEPA}H$), 4.56 (1H, m, H_{Cp}), 4.51 (1H, m, H_{Cp}), 4.23 (2H, s, H_{Cp}), 4.00 (5H, s, H_{Cp}), 3.89 (1H, m, C$_\alpha H$), 2.58–2.44 (2H, m, C$_\beta H_2$), 2.15–1.95 (2H, m, CH_2CH$_3$), 1.45–1.30 (2H, m, CH_2CH$_3$), 0.92 (3H, t, J = 7 Hz, CH$_2$CH_3), 0.63 (3H, t, J = 7 Hz, CH$_2$CH_3). ^{13}C NMR ($CDCl_3$): 169.6 and 169.2 (*C*O) and (Fc–*C*O), 136.4, 129.3 128.9, 126.8 (C_{Phe}), 137.7–135.9 (6C, C_{ipso}), 134.2–133.7 (12C, C_{ortho}), 129.5–129.0 (6C, C_{para}), 128.2–127.7 (12C, C_{meta}), 135.8 (H*C*≡C(Pt)), 110.6 (HC≡*C*(Pt)), 76.1, 70.2, 69.8, 68.4, 67.8 (C_{Cp}), 53.3 (C_α), 38.7 (C_β), 30.8 and 30.3 (*C*H$_2$CH$_3$), 9.2 and 9.1 (CH$_2$*C*H$_3$). ^{15}N NMR ($CDCl_3$): –268

(NH_{Phe}), −245 (NH_{DEPA}). ESI-MS (positive, CH_2Cl_2): *m/z* 1190 ($[M + H]^+$).

Ferrocene phenylalanine methyl ester (5). **5** was prepared following the procedure published by Herrick, Jarret and Curran *et al.*[42] The spectroscopic data of the product matched that reported previously.[42,43]

Synthesis of *N*-Boc-protected propargylamide T-PNA monomer (6). HBTU (0.12 g, 0.32 mmol) was added to a solution of Boc-T-PNA-OH (0.1 g, 0.32 mmol), propargylamine (0.02 g, 0.32 mmol) and NEt_3 (0.07 g, 0.64 mmol) in acetonitrile. After 15 min of stirring at room temperature, brine (10 mL) was added, the organic phase was separated, the aqueous layer was extracted with EtOAc and the combined organic phases were washed with 2 M $HCl_{(aq)}$, water, sat. $NaHCO_{3(aq)}$ and water. After drying over Na_2SO_4 and filtration, all solvents were removed *in vacuo* and **6** was obtained as a white solid (0.13 g, 95%). ^{1}H NMR (CD_3CN): 9.5 (1H, s, NH_T), 7.21/7.03 (1H, s, br, NH_{CO}), 7.09/7.08 (1H, s, C=CH), 5.9/5.45 (1H, s, br, NH_{BOC}), 4.56/4.42 (2H, s, CH_2), 4.03/3.92 (2H, s, CH_2), 4.04/3.91 (2H, s, C$H_{2,alkyne}$), 3.41/3.37 (2H, m, CH_2CH$_2$NH), 3.25/3.12 (2H, m, CH$_2$CH_2NH), 2.48/2.44 (1H, t, CH_{alkyne}), 1.81 (s, 3H, C$H_{3,T}$), 1.39 (s, 9H, C$H_{3\,BOC}$). ^{13}C NMR (CD_3CN): 171.7 (*C*O), 169.3/168.7 (*C*O), 165.3 (CO$_T$), 157 (*C*O$_{BOC}$), 152.4 (HC=*C*), 142.7 (H*C*=C), 80.9 (C_{alkyne}), 79.9 ($C_{BOC}(CH_3)_3$), 72.1/72.4 (HC_{alkyne}), 51.5/50.9 (CH_2), 49.4/49.3 (CH_2), 49.2/48.9 (*C*H$_2$CH$_2$NH), 39.3/38.8 (CH$_2$*C*H$_2$NH), 29.9 (*C*H$_{3,BOC}$), 14.5 (*C*H$_{3,T}$). ^{15}N NMR (d_6-DMSO): −224 (N_TH), −272 (*N*H). IR: 3435 (m), 1686 (s), 560 (w). Raman: 2123. ESI-MS (positive, CH_3OH): *m/z* 422 $[M + H]^+$, 439 $([M + NH_4]^+$, 860 $[2M + NH_4]^+$.

Synthesis of propargylamide T-PNA monomer (7). **6** (0.50 g, 1.22 mmol) was stirred in a mixture of TFA–CH_2Cl_2 (9 : 1 v/v) (20 mL) for 15 min at room temperature before all the volatiles were evaporated to dryness. The residual oil was then again stirred in a mixture of TFA–CH_2Cl_2 (9 : 1 v/v) (20 mL) for 15 min at room temperature. After evaporation of the volatiles, dry diethyl ether (20 mL) was added to the residual oil and the mixture stirred for 5 min at room temperature. The reaction mixture was again evaporated to dryness. **7** was isolated as a white, hygroscopic solid and was used without further purification to the next synthetic step.

Synthesis of ferrocene-propargylamide T-PNA monomer 8. To a solution of **7** (73.8 mg, 0.24 mmol) and ferrocene carboxylic acid (0.05 g, 0.24 mmol) in CH_3CN, NEt_3 (0.05 g, 0.48 mmol) and HBTU (0.09 g, 0.24 mmol) were added to the reaction mixture. Brine (10 mL) was added after 15 min of stirring at room temperature and after another 20 min of stirring, the organic phase was separated and the aqueous layer extracted with $CHCl_3$. The organic phase was washed with 2 M HCl, H_2O, saturated $NaHCO_3$ and H_2O. After drying over $MgSO_4$ and filtration, all volatiles were removed *in vacuo*, yielding **8** (0.11 g, 89%). ^{1}H NMR (CD_3CN): 9.16/9.12 (1H, br, N*H*), 7.28/7.26/7.03/6.90 (all N*H*), 7.05/6.87 (1H, s, C=C*H*), 4.71/4.62 (2H, pseudo-t, H_{Cp}), 4.57/4.44 (2H, s, CH$_2$), 4.36/4.32 (2H, pseudo-t, H_{Cp}), 4.19/4.17 (5H, s, H_{Cp}), 4.09/3.97 (2H, s, CH_2), 4.00/3.97 (2H, m, CH_2–C$_{alkyne}$), 3.52/3.38 (2H, m, CH_2CH$_2$NH), 3.52/3.26 (2H, m, CH$_2$CH_2NH), 2.45/2.48 (1H, s, HC_{alkyne}) 1.75/1.74 (3H, s, C$H_{3,T}$). ^{13}C NMR (CD_3CN): 171.3 (*C*=O$_{PROP}$), 170.8 (Cp–*C*=O), 168.5 (*C*=O), 165.1 (*C*O$_T$), 165.0 (CO$_T$), 152 (HC=*C*), 142.5 (H*C*=C), 79.2/79.1 (C_{alkyne}), 72.4/72.3 (HC_{alkyne}), 72.0/71.4/71.08/70.6/69.2/69.0 (C_{Cp}), 51.3/51.0 (*C*H$_2$), 49.3/49.2 (*C*H$_2$CH$_2$NH), 49.0/48.6 (CH_2), 38.1/38.0 (CH$_2$*C*H$_2$NH), 29.6/29.2 (*C*H$_2$–C$_{alkyne}$), 12.3 (*C*H$_{3,T}$). ^{15}N NMR (CD_3CN): −226 (NH_T), −272 (*N*H), −275(*N*H). IR: 3449 (m), 1676 (s), 1535 (m), 1407 (w), 1222 (w). Raman: 2113. UV (CH_3CN): 255 (450 nm), 14700 (264 nm). MS: *m/z* 533 (86), 376 (100), 213 (28), 95 (27), 65 (31%).

Ferrocene–Pt(0)–propargylamide T-PNA monomer 9. A solution of $(C_2H_4)Pt(PPh_3)_2$ (0.14 g, 0.19 mmol) in degassed THF (20 mL) was added dropwise under Ar to a solution of alkyne **8** (0.10 g, 0.19 mmol) in degassed THF (20 mL). After evolution of gas had ceased, stirring was continued for an additional hour and all volatiles were removed from the reaction mixture *in vacuo*. The product appeared rather pure by ^{1}H NMR spectroscopy, but analytically pure samples were obtained by HPLC, yielding **9** (80 mg, 33%). ^{1}H NMR (d_6-DMSO): 11.25 (1H, br, NH_T), 8.55/8.25 (1H, br, N*H*), 8.05/7.75 (1H, br, N*H*), 7.31–7.18 (31H, m, H_{PPh_3} and C=C*H*), 6.58–6.44 (1H, dd, CH_{Alkyne}), 4.75/4.71 (2H, pseudo-t, H_{Cp}), 4.72/4.47 (s, 2H, CH_2), 4.29/4.28 (pseudo-t, 2H, H_{Cp}), 4.16/4.10 (s, 5H, H_{Cp}), 4.11/3.93 (s, 2H, H_{Cp}), 3.82/3.78 (m, 2H, C$H_{2,alkyne}$), 3.44/3.30 (m, 4H, CH_2CH$_2$NH and CH$_2$CH_2NH), 1.73/1.70 (s, 3H, C$H_{3,T}$). ^{13}C NMR (d_6-DMSO) : 141.8 (H*C*=C), 133.1/129.1/127.7 (C_{PPh_3}), 69.2/67.7 (C_{Cp}), 49.9/48.9 (*C*H$_2$), 47.7 (CH$_2$), 39.6 (CH$_2$*C*H$_2$NH), 36.9 (*C*H$_{2,Alkyne}$), 11.6 (*C*H$_3$). ^{31}P NMR (d_6-DMSO): 29.6/26.8 (ma, $^2J_{P1–P2}$ = 31.5 Hz, $^1J_{Pt–P}$ = 3504 and 3558 Hz), 29.8/26.2 (mi, $^2J_{P1–P2}$ = 31.6 Hz, $^1J_{Pt–P}$ = 3502 and 3557 Hz). ESI-MS (positive, CH_3CN–THF): *m/z* 1252 $[M]^+$. IR: 1685 (s), 1535 (w), 695 (m).

X-Ray crystallographic data collection and refinement of the structures

Yellow–orange single crystals of **3a** and **4b** were coated with perfluoropolyether, picked up with nylon loops and were mounted in the nitrogen cold stream of a Nonius KappaCCD and a Siemens SMART diffractometer, respectively. Graphite-monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å) was used throughout. Final cell constants were obtained from least squares fits of several thousand strong reflections. Intensity data were corrected for absorption using intensities of redundant reflections. The structures were readily solved by Patterson methods and subsequent difference Fourier techniques. The Siemens ShelXTL[59] software package was used for solution and artwork of the structures, ShelXL97 was used for the refinement. All non-hydrogen atoms were anisotropically refined and hydrogen atoms were placed at calculated positions and refined as riding atoms with isotropic displacement parameters. Crystallographic data of the compounds are listed in Table 1.

Diffraction data quality of **3a** was found to be low due to the crystal quality indicated by weak diffraction and a high mosaicity of 1.2°. Data were collected to a 2θ angle of 55° but a data cut-off was applied at 45° (R_{int} = 0.21) since the data quality at higher angles was out of limits. Structure solution and refinement of compound **3a** was performed in enantiomorphic space groups $P3_121$ (no. 152) and $P3_221$ (no. 154). Though the diffraction data quality is not superb, space group assignment was unambiguously possible. The Flack parameter[60] for a refinement in $P3_121$ gave a value close to 0 (−0.03(4)) whilst the parameter refined to a value

Table 1 Crystallographic data for **3a** and **4b**

	3a	**4b**
Formula	$C_{23}H_{22}FeN_2O_2$	$C_{63}H_{60}FeN_2O_2P_2Pt$
M_r	414.28	1190.01
Crystal size/mm	$0.32 \times 0.14 \times 0.14$	$0.44 \times 0.14 \times 0.14$
Crystal system	Trigonal	Monoclinic
Space group	$P3_121$ (no. 152)	$P2_1$ (no. 4)
a/Å	9.6860(10)	16.116(2)
b/Å	9.6860(10)	18.556(2)
c/Å	36.733(5)	19.210(3)
β/°	90	111.24(2)
V/Å^3	2984.5(6)	5354.5(12)
Z	6	4
T/K	100(2)	100(2)
D_c/g cm^{-3}	1.383	1.476
Refl. collected ($2\Theta_{max}$/°)	6782 (45.00)	52151 (60.00)
Unique refl. (with $I > 2\sigma(I)$)	2560 (1845)	24746 (18101)
R_{int}	0.2138	0.0470
No. params/restr.	253/0	1283/1
λ(Mo-Kα)/Å	0.71073	0.71073
μ(Mo-Kα)/cm^{-1}	7.79	29.86
$R1^a$/goodness of fit^b	0.0694/1.063	0.0452/0.935
$wR2^c$ ($I > 2\sigma(I)$)	0.1166	0.0975
$\Delta\rho$(max./min.)/e Å^{-3}	+0.48/−0.43	+1.54/−2.21

^{a} Observation criterion: $I > 2\sigma(I)$. $R1 = \sum\|F_o| - |F_c\|/\sum|F_o|$. ^{b} GOF = $[\sum[w(F_o^2 - F_c^2)^2]/(n-p)]^{1/2}$. ^{c} $wR2 = [\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]]^{1/2}$ where $w = 1/\sigma^2(F_o^2) + (aP)^2 + bP$, $P = (F_o^2 + 2F_c^2)/3$.

of about 1.0 upon space group change to $P3_221$. The *R*-factors were also slightly better for the first choice. Atomic displacement parameters of the Cp-ring carbon atoms containing C(21) to C(25) were restrained using the SIMU instruction of ShelXL97.

Compound **4b** crystallizes in chiral space group $P2_1$ (no. 4) with two crystallographically independent molecules per asymmetric unit. Due to a pseudo-centrosymmetric packing of these molecules, the space group appeared first to be $P2_1/c$ (no. 14). Reflections fulfilling the extinction requirements for a *c*-glide plane were found to be weak, but a considerable number of them were observed using the standard 3σ criterion. Nevertheless, a refinement in $P2_1/c$ was initially performed and seemed to work well, but resulted in a disorder of the chiral C-atom in the phenylalanine unit of the molecule. Refinement in $P2_1$ yielded two independent molecules with the expected L-amino-acid configuration and a Flack parameter of –0.029(7). Atomic displacement parameters of the phenyl-ring carbon atoms C(151) to C(156) and carbon atoms C(212) and C(213) were restrained using the DELU instruction of ShelXL97.

Abbreviations

CLEC	cross-linked enzyme crystals
ESI-MS	electrospray ionisation mass spectrometry
Fc	Ferrocenyl ((η-C_5H_4)Fe(η-C_5H_5))
HBTU	*O*-(1*H*-Benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyl-uronium hexafluorophosphate
ma	major
mi	minor
Phe	phenylalanine
PNA	peptide nucleic acid
TFA	trifluoroacetic acid

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