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Transition metal complexes as linkers for solid phase synthesis: chromium carbonyl complexes as linkers for arenes

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Substrates containing aromatic rings have been attached to 'polymer supported triphenylphosphine' using a chromium carbonyl linker, chemically manipulated, and released from the polymer to demonstrate the potential use of π-bound ligands in linker chemistry. Immobilisation of the phenylalanine derivative Fmoc-Phe-O*t*Bu *via* its aromatic ring has been achieved and the resulting resin successfully subjected to standard amino acid deprotection and coupling procedures.

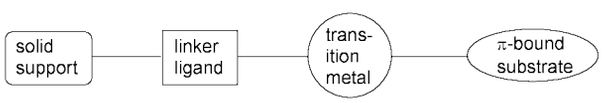
Introduction

Combinatorial chemistry and multiple parallel synthesis are now established as invaluable approaches to the production of large numbers of compounds.[1] Using polymer supported (or 'solid phase') synthesis, the development of combinatorial chemistry has reached a stage where vast 'libraries' of organic compounds may be stored and processed with relative ease. The efficiency of solid phase techniques has led to the use of automation in organic synthesis to an unprecedented degree.

Substrate molecules are generally attached to the polymer *via* a covalent bond. Once attached, the immobilised substrate may be isolated simply by filtration of the polymer from the reaction mixture. Further organic transformations may then be carried out while the substrate is bound to the polymer before chemical cleavage of the final product from the solid support. A legacy of solid phase peptide synthesis (SPPS) is the release of carboxylic acid derivatives from an ester or amide-bound substrate. While entirely appropriate in peptide synthesis, these polar functionalities are not always desirable in a more general arena. Efforts to address this problem have, in recent years, stimulated the evolution of an impressive arsenal of linkers with the ability to release most functionalities upon cleavage.

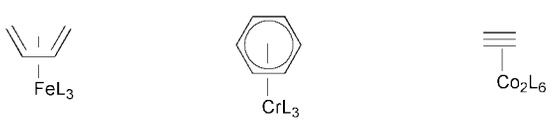
Ubiquitous in organic chemistry is the unsaturated carbon scaffold, the arene in particular, and a number of linkers have been developed which liberate such functionality. An elegant example is the attachment of aromatic rings to a polymer support *via* aryl–silicon bonds that, upon cleavage with anhydrous HF, afford a product containing an aryl–hydrogen bond.[2]

We reasoned that a substrate could be attached to a solid support by a method other than a conventional σ-bond. Many organic molecules containing an unsaturated moiety may be complexed with transition metals *via* a bonding mode described by the Dewar–Chatt model. Donation of π electrons from the unsaturated organic molecule into empty d_σ orbitals on the metal is accompanied by donation from filled metal d_π orbitals into empty π* orbitals on the organic molecule. Futhermore, decomplexation may often be achieved without any alteration to the organic species. Examples of compounds which fulfil these criteria include diene–iron, **1**, arene–chromium, **2**, and alkyne–cobalt, **3**, complexes. Due to the variety of ligands which complex with transition metals, it is possible to bind transition metal species such as **1**–**3** to a polymer *via* a



Scheme 1

'linker ligand' (Scheme 1). Subsequent chemical transformations could then be carried out without cleavage of the substrate and, finally, decomplexation conditions would afford a transformed organic molecule bearing the intact unsaturated carbon scaffold. We describe herein experiments that demonstrate for the first time that this approach to immobilising and releasing organic molecules is feasible. Part of this work has been described in a preliminary communication.[3]



1 **2** **3**

Results and discussion

Aromatic rings are one of the most common functionalities in organic molecules and most may be complexed to chromium carbonyl moieties.[4] Moreover the complexes are resistant to the conditions of many synthetic reactions, and yet may be decomplexed easily under several sets of well-defined conditions. A polystyrene-supported phosphine, 'triphenylphosphine, polymer-bound' (PTPP) is commercially available and relatively inexpensive. As substitution of tricarbonyl(arene)chromium(0) complexes with phosphines is well established,[5] it was envisaged that the phosphines of this polymer would function as suitable linker ligands between the polystyrene and the chromium metal. The phosphorus loading of the commercial polymer (1.6 mmolP g^{-1}) equates to a pendant diphenylphosphine moiety approximately every 4.2 styrene units. The polystyrene backbone is cross-linked with 1% divinylbenzene, a percentage which imparts structural rigidity and strength while also permitting partial solvation to occur.[6] The colourless resin beads have good swelling properties in widely used solvents such as THF, DCM and DMF, and poor swelling properties in aliphatic hydrocarbons and diethyl ether. We thus decided to

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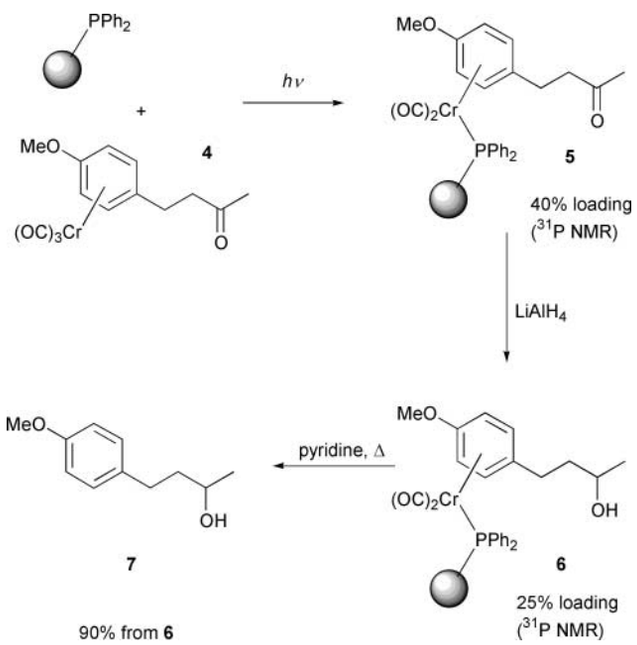
attempt to immobilise an (arene)tricarbonylchromium(0) complex onto PTPP, demonstrate that the immobilised organic molecule could be manipulated whilst bound to the resin *via* the metal, and then remove the modified organic product from the resin.

Commercially available 4-(4-methoxyphenyl)butan-2-one was heated with hexacarbonylchromium(0) to give the novel complex **4** as yellow air-stable crystals in 71% yield. Complex **4** (1.1 equivalents) was then irradiated in the presence of PTPP in THF. Subsequent filtration, washing and drying of the polymer gave a brown powder that was characterised as predominantly **5** on the basis of its IR and ^{31}P NMR spectra (Scheme 2).



Scheme 2

The former contained strong absorptions at 1870, 1802 cm^{-1} [$Cr(CO)_2PPh_3C_6H_5OMe$[7] strongly absorbs at 1886 and 1827 cm^{-1}] and 1710 cm^{-1}, whilst the latter contained a resonance at δ 90 [$Cr(CO)_2PPh_3C_6H_5OMe$ resonates at δ 91.9[7]]. The ^{31}P NMR spectrum revealed that the polymer coverage with the arene chromium dicarbonyl complex was ~40%, the remainder of the sites being made up of polymer–$PPh_2Cr(CO)_5$ ($\delta = 56$, 20%), polymer–$P(O)Ph_2$ ($\delta = 29$, 10%) and polymer–PPh_2 ($\delta = -5$, 30%) [$PPh_3Cr(CO)_5$, $\delta_P = 55.3$;[8] polymer–$P(O)Ph_2$, $\delta_P = 28.8$;[9] polymer–PPh_2, $\delta_P = -6.3$[9]]. Polymer **5** was then reduced with $LiAlH_4$ giving, after work-up, a dark yellow powder that did not absorb at 1710 cm^{-1}. The ^{31}P NMR spectrum of the reduced material revealed that the loading of **6** on the polymer was 25% indicating some loss of material from the polymer, perhaps as a result of complex decomposition resulting from nucleophilic addition at the metal carbonyl ligands, and representing a yield for this step of 62%. The reduction product was released from the polymer by heating in pyridine for 2 h. Filtration, washing the polymer with THF and diethyl ether, and concentration of the washings gave alcohol **7** of ≥95% purity. The yield for the release of **7** from the polymer was 92%.

The above experiments demonstrate that an organic molecule containing an aromatic ring can be attached to a solid support *via* a transition metal–ligand linker, manipulated and subsequently released. Each step in the sequence proceeded in tolerably good yield (unoptimised). Most encouraging at this stage, however, was the usefulness of IR and ^{31}P NMR spectroscopy for obtaining direct information about the structure and loading of polymer-bound complexes **5** and **6**.

We next turned out attention to the immobilisation of the biologically important molecule phenylalanine *via* a transition metal–ligand linker with a view to determining whether or not the arene immobilised amino acid could be manipulated on the polymer, and products from its reactions subsequently released. The orthogonally protected phenylalanine derivative Fmoc-Phe-O*t*Bu **8** was prepared by treatment of L-phenylalanine *tert*-butyl ester hydrochloride with *N*-[(fluoren-9-ylmethoxycarbonyl)oxy]succinimide, FmocOSu (Scheme 3).[10] The Fmoc protecting group was attractive not only as perhaps the most widely used protocol for SPPS, but also for the ease with which the carbamate is cleaved non-hydrolytically using simple amines, releasing the protected amine as its free base. After disappointing preliminary results with other Phe derivatives, these attractions were seen to outweigh any complications that might arise from the aromatic nature of the Fmoc group in the complexation step.

As anticipated, direct complexation of Fmoc-Phe-O*t*Bu **8** with hexacarbonylchromium(0) gave the desired complex **9** in 31% yield accompanied by the tricarbonyl(η^6-dibenzofulvene)chromium(0) **10** in 16% yield. The photolytic loading of the Fmoc-protected derivative **9** onto polymer-bound triphenylphosphine was effected by irradiation in THF followed by filtration, washing and drying of the polymer beads. Analysis of the resulting resin by ^{31}P NMR and IR spectroscopy revealed that the desired resin-bound arene species **11** was found to occupy 70% of the phosphine sites, equating to a loading of 0.69 mmol[Fmoc-Phe-O*t*Bu] g^{-1}. [The remaining phosphine sites were either unreacted phosphine (10%), phosphine oxide (15%), polymer–$(PPh_2)_2Cr(CO)_4$ (5%) or polymer–$PPh_2Cr(CO)_5$.]

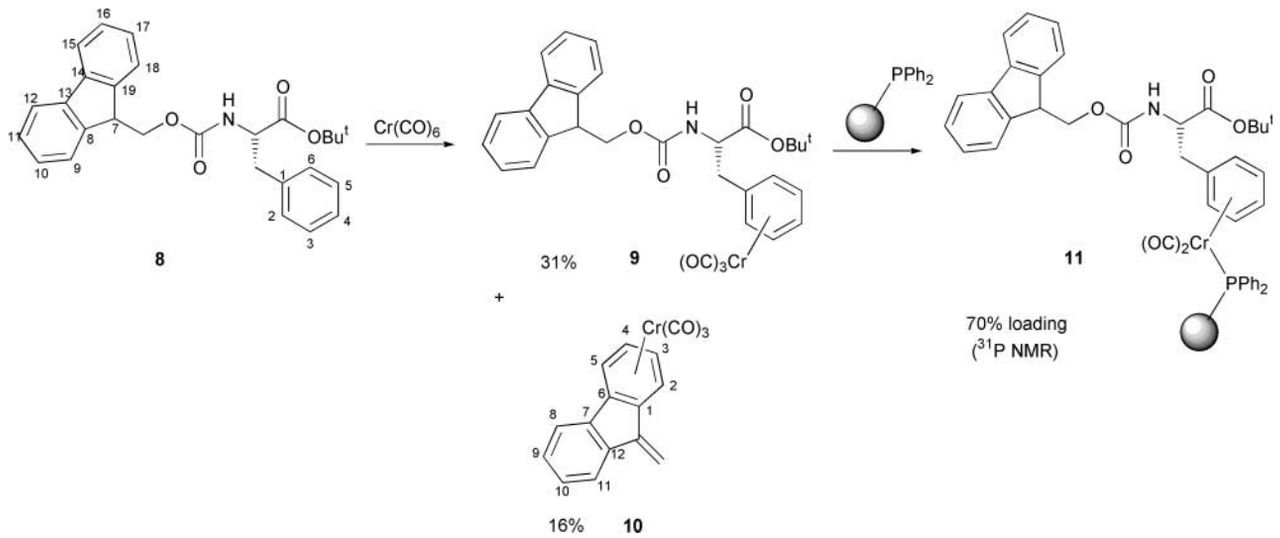
Having successfully immobilised a phenylalanine derivative with an orthogonal protecting set, experiments were undertaken to assess the stability of the carbonylchromium(0) linker in the context of established peptide chemistries. Our efforts were directed towards deprotection of, and subsequent coupling at, the N-terminus. Hence to the resin beads **11** suspended in DCM under constant nitrogen agitation was added piperidine (Scheme 4). After 20 minutes the beads were filtered and washed, and the process repeated. Resin **12** bearing the free amine was resuspended in DCM and acetylated with excess triethylamine and acetic anhydride to give resin-bound Ac-Phe-O*t*Bu **13**. ^{31}P NMR spectroscopy of the resin revealed an 8% loss in occupancy of phosphine sites by the (η^6-Ac-Phe-O*t*Bu)dicarbonyl(phosphine)chromium(0) linker equating to a loading of 0.71 mmol[Ac-Phe-O*t*Bu] g^{-1}. IR spectroscopy data were consistent with the integrity of the linker and with formation of the amide, identified by an additional absorption at 1677 cm^{-1}.

Cleavage of the linker to liberate the product Ac-Phe-O*t*Bu **14**[11] was effected by stirring the resin **13**, ground to a fine yellow powder, in DCM in air under white light for 48 h. Filtration of the mixture through Celite to remove the resulting green–brown polymeric residue gave a colourless filtrate containing, as indicated by ^{1}H NMR spectroscopy, **14** and minor unidentified hydrocarbon and aromatic contaminants, possibly fragments of the polystyrene resin. Peaks characteristic of Fmoc-Phe-O*t*Bu **8** were absent from the spectrum confirming that deprotection of the amine of **11** is complete under the conditions used. The crude mixture was purified by chromatography and **14** was isolated in 77% yield (68% overall from resin **11**). The optical rotation of released **14** was within 2° of that quoted in the literature, demonstrating that the linker methodology did not affect the optical purity of the amino acid.

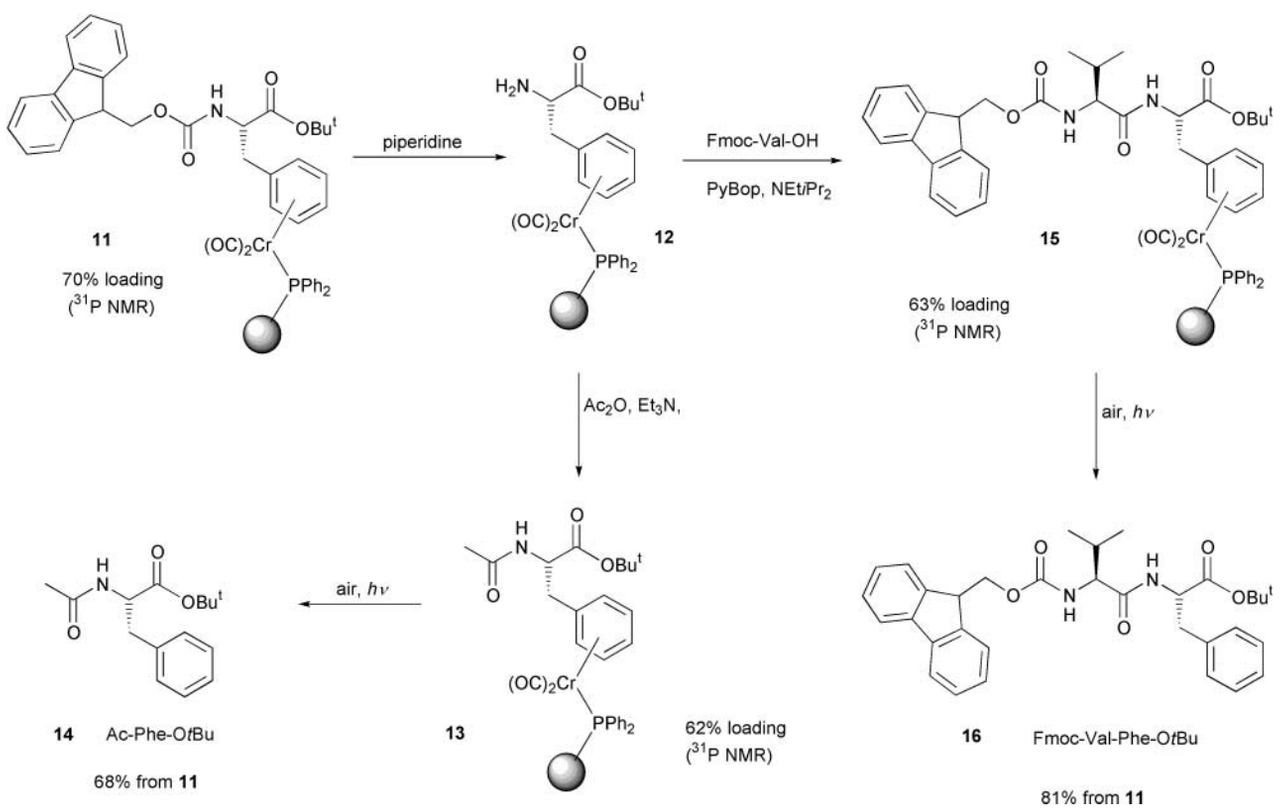
Having demonstrated that deprotection and chemical manipulation of the N-terminus is feasible, peptide coupling conditions were investigated next. Amine deprotection of resin **11** and isolation of resin **12** were carried out as described above. Of the wide variety of peptide coupling conditions available, it was decided to use the *in situ* activating agent benzotriazolyloxytripyrrolidinophosphonium hexafluorophosphate, PyBOP[12]. Developed as a substitute to the widely-

used and highly efficient benzotriazolyloxytris(dimethylamino)-phosphonium hexafluorophosphate (BOP), PyBOP reacts without the generation of carcinogenic HMPA. Hence, to a suspension of **12** in DCM was added a solution of diisopropylethylamine and Fmoc-Val-OH in DCM. Following addition of PyBOP, the mixture was left under constant nitrogen agitation for 6 h, then filtered and washed in the usual way. ^{31}P NMR spectroscopic analysis of the resulting resin-bound dipeptide **15** revealed a 63% phosphorus site occupany, equating to a 10% loss over two steps and a substrate loading of 0.60 mmol-[Fmoc-Val-Phe-O*t*Bu] g^{-1}. Aerial oxidative cleavage of the chromium(0) linker effected release of the protected dipeptide Fmoc-Val-Phe-O*t*Bu **16** in 90% yield. Comparison of IR, ^{1}H and ^{13}C NMR and mass spectroscopic data with those from **16** prepared by conventional solution phase chemistry confirms the product's identity and a comparison of the optical rotations of both materials (values within 4°) supports retention, to a large extent, of optical purity.

The experiments described above demonstrate that transition metal π-complexes may be used as linkers in solid phase synthesis. Although the focus of our first experiments in this area has been the attachment of arene groups to a phosphine-containing polymer *via* a chromium carbonyl linker, several other possibilities exist, including those indicated by structures **1** and **3**, for the immobilisation of common organic motifs *via* this approach. Further support for the use of transition metal linkers has recently been provided by Maiorana *et al*. who have developed an attractive chromium(0) linker using a tethered isocyanide, a ligand electronically very similar to carbon monoxide. The S_NAr reaction between a dicarbonyl(fluoroarene)(polymer-bound isocyanide)chromium(0) complex and a variety of nitrogen nucleophiles was effected with high yields.[13]



Scheme 3



Scheme 4

Experimental

Reactions under nitrogen were performed using standard vacuum line and Schlenk tube techniques.[14] Diethyl ether, toluene and hexane were dried over sodium wire. THF was distilled from sodium benzophenone ketyl. DCM and 1,4-dioxane were distilled from calcium hydride. All solvents intended for use in chromatography were used as bought. SiO_2 refers to chromatography grade silica of particle size 40–63 μm. Irradiation was carried out with a 125 W Hg vapour lamp (Cathodeon). Melting points, which are uncorrected, were determined using a Gallenkamp capillary melting point apparatus. IR spectra were obtained on a Perkin-Elmer 1710FTIR spectrometer. NMR spectra were recorded at room temperature on Bruker DRX300 (300.0 MHz ^{1}H, 75.5 MHz ^{13}C), Bruker DRX500 (500.0 MHz, ^{1}H, 202.4 MHz ^{31}P) (Imperial College) and Bruker AM360 (360.0 MHz ^{1}H, 90.6 MHz ^{13}C, 145.8 MHz ^{31}P), Bruker AMX400 (400.0 MHz ^{1}H, 100.6 MHz ^{13}C) (King's College) and Bruker DPX300 (300.0 MHz ^{1}H, 75.5 MHz ^{13}C) (AstraZeneca UK Ltd.). Resin samples for NMR were prepared under N_2, were swollen in deoxygenated THF and were scanned with a D_2O capillary lock. Longitudinal relaxation times of the ^{31}P nuclei were determined using the inverse recovery technique. Phosphine oxide and transition metal-complexed phosphines were found to have similar relaxation times of ~0.07 seconds. The free phosphine was generally too weak to be measured accurately but, by inspection, appeared to have a slightly longer relaxation time of 0.10–0.15 seconds. Based on these figures, a 90° pulse was applied with a relaxation delay of 0.3 seconds. Because resin signals can be broad the FID (free induction decay) decays rapidly and only a short acquisition time is required, achieved by data set reduction to between 64 and 1024 words (depending on the sample). As a means to reduce 'ringing' in the spectra, a trapezoidal window function was used to reduce the last third of the FID to zero and the remaining data set (4 K words) was 'zero filled'. Mass spectra were recorded on VG Micromass 7070E and AutoSpec-Q instruments at Imperial College, on a VG 70/250 SE spectrometer at AstraZeneca UK Ltd. and on Kratos MS890MS and JEOL AX505W instruments at King's College London. Microanalyses were conducted by the Imperial College of Science, Technology and Medicine microanalytical service, by Steven Boyer (S.A.C.S.) at the University of North London and by MEDAC Ltd., Analytical and chemical consultancy services, Brunel Science Centre. Optical rotation values were measured at 589 nm on a Perkin-Elmer 241 polarimeter using a cell of 1 dm pathlength and are reported in 10^{-1} deg cm^2 g^{-1}.

[4-(4-Methoxyphenyl)butan-2-one]tricarbonylchromium(0) 4

Hexacarbonylchromium(0) (2.50 g, 11.4 mmol) was dissolved in degassed dibutyl ether (80 cm^3), and to this mixture was added 4-(4-methoxyphenyl)butan-2-one (3.03 g, 17.0 mmol) in degassed THF (8 cm^3). The reaction vessel was fitted with an air condenser below a water condenser. The reaction mixture was then heated to 140 °C for 48 h with complete exclusion of light, after which time solvents were removed *in vacuo*. The residual green sludge was filtered through deactivated alumina (diethyl ether). The yellow oil obtained was preabsorbed onto silica gel and purified by column chromatography [SiO_2; petrol–diethyl ether (1 : 1), then diethyl ether], which yielded a yellow solid. This was subsequently recrystallised [hexane–diethyl ether (10 : 1)] to yield the *title complex* **4** as yellow crystals (2.54 g, 71%); mp 54–55 °C (Found: C, 53.7; H, 4.5. $C_{14}H_{14}CrO_5$ requires C, 53.51; H, 4.49%); ν_{max}(dichloromethane)/cm^{-1} 1957vs, 1863vs [Cr(C≡O)$_3$] and 1714s (C=O); δ_H(270.0 MHz, $CDCl_3$) 2.20 (3 H, s, MeCO), 2.56 (2 H, t, *J* 7, CH_2CO), 2.75 (2 H, t, *J* 7, $ArCH_2$), 3.70 (3 H, s, MeO), 5.13 (2 H, d, *J* 7, MeOCCHC*H*), and 5.54 (2 H, d, *J* 7, MeOCC*H*); $\delta_C\{^1H\}$(75.4 MHz, $CDCl_3$) 27.5 (*C*H$_3$CO), 30.4 (*C*H$_2$CO), 45.3 (ArCH$_2$), 56.1 (MeO), 78.2 (MeOCCH*C*H), 96.3 (MeOC*C*H), 105.5 (MeOCCHCH*C*), 142.8 (MeO*C*), 207.1 (C=O) and 233.8 (C≡O); *m*/*z* (E.I.) 314 (M$^+$, 5%), 286 (M − CO, 7), 258 (M − 2CO, 3), 230 (M − 3CO, 100), 215 (M − 3CO − Me, 20), 178 [M − Cr(CO)$_3$, 15], and 121 (MeOC$_7$H$_6$, 80).

[4-(4-Methoxyphenyl)butan-2-one]dicarbonyl(triphenylphosphine polymer)chromium(0) 5

Triphenylphosphine polymer (3 mmol g^{-1}, 1.59 g, 4.77 mmol) was stirred in THF (350 cm^3) for 1 h before addition of [4-(4-methoxyphenyl)butan-2-one]tricarbonylchromium(0) **4** (1.65 g, 5.25 mmol). The mixture was irradiated for 3 h, and then allowed to react in the dark for a further 1 h. The reaction mixture was transferred by cannula into a 1 dm^3 round-bottomed flask, and the solid allowed to settle. The supernatant solvent was removed by cannula, and the residual solid washed with THF (2 × 100 cm^3). The solid was then dried *in vacuo*, and the *title polymer* **5** isolated as a brown powder (2.3 g); ν_{max}(Nujol)/cm^{-1} [polymer–PPh$_2$Cr(CO)$_2$Ar] 1870s, 1802s [Cr(C≡O)$_3$] and 1710s (C=O); [polymer–PPhCr(CO)$_5$] 2059m, 1984w and 1933s [Cr(C≡O)$_3$]; $\delta_P\{^1H\}$(202.4 MHz, $CDCl_3$) −5 (30%, polymer–PPh$_2$), 29 (10%, polymer–PPh$_2$=O), 56 [20%, polymer–PPh$_2$Cr(CO)$_5$], 90 [40%, polymer–PPh$_2$Cr(CO)$_2$Ar]. ^{31}P NMR analysis determined polymer loading with Ar(CO)$_2$Cr as 1.20 mmol g^{-1}.

[4-(4-Methoxyphenyl)butan-2-ol]dicarbonyl(triphenylphosphine polymer)chromium(0) 6

[4-(4-Methoxyphenyl)butan-2-one]dicarbonyl(triphenylphosphine polymer)chromium(0) **5** (1.2 mmol g^{-1}, 40% load), 1 g, 1.2 mmol] was stirred in THF (80 cm^3) for 1 h, and then cooled to 0 °C. Lithium aluminium hydride (137 mg, 3.61 mmol) was dissolved in THF (10 cm^3), and the solution added dropwise to the polymer suspension *via* a cannula. The mixture was allowed to warm to room temperature, and stirred for 16 h. Ethyl acetate (10 cm^3) was cautiously added, followed by water (10 cm^3), and the mixture allowed to settle. The supernatant liquid was removed by cannula, and the remaining solid washed with THF (2 × 20 cm^3) and diethyl ether (20 cm^3). The solid was dried *in vacuo*, and the *title polymer* **6** isolated as a dark yellow powder (0.93 g); ν_{max}(Nujol)/cm^{-1} [polymer–PPh$_2$Cr(CO)$_2$Ar] 1876s, 1814s [Cr(C≡O)$_3$], complete absence of ketone absorption at 1710 cm^{-1}; [polymer–PPh$_2$Cr(CO)$_5$] 2060vw and 1929vw [Cr(C≡O)$_3$]; $\delta_P\{^1H\}$(202.4 MHz, $CDCl_3$) −21 (55%, polymer–PPh$_2$), 22 (20%, polymer–PPh$_2$=O), 54 [trace, polymer–PPh$_2$Cr(CO)$_5$], 86 [25%, polymer–PPh$_2$Cr(CO)$_2$Ar]. ^{31}P NMR analysis determined polymer loading with Ar(CO)$_2$Cr as 0.72 mmol g^{-1}.

4-(4-Methoxylphenyl)butan-2-ol 7

[4-(4-Methoxyphenyl)butan-2-ol]dicarbonyl(triphenylphosphine polymer)chromium(0) **6** [0.72 mmol g^{-1}, 25% load, 500 mg, 0.36 mmol] was added to pyridine (10 cm^3), the mixture degassed and subsequently refluxed under a nitrogen atmosphere for 2 h, during which time the solution became bright red. The mixture was allowed to cool, and the solid to settle out. Supernatant liquid was removed *via* a cannula, and the residual solid was washed successively with THF (2 × 20 cm^3) and diethyl ether (20 cm^3). The organic washings were reduced *in vacuo* and filtered through a short pad of silica (diethyl ether). Diethyl ether was removed *in vacuo* to afford the title compound **7**[15] as a colourless oil of ≥95% purity (60 mg, 0.33 mmol, 92%); δ_H(270.0 MHz, $CDCl_3$) 1.24 [3 H, d, *J* 6, CH(OH)C*H*$_3$], 1.68–178 [3H, m, C*H*$_2$CH(OH) and OH], 2.58–2.76 (2H, m, $ArCH_2$), 3.81 (3H, s, OCH_3), 3.82–3.86 (1H, m, CHOH), 6.85 (2H, d, *J* 8.5, MeOCC*H*), and 7.14 (2H, d, *J* 8.5, MeOCCHC*H*).

Fmoc-Phe-O*t*Bu 8

To a mixture of L-phenylalanine *tert*-butyl ester hydrochloride (3.05 g, 11.9 mmol) and *N*-[(fluoren-9-ylmethoxycarbonyl)-oxy]succinimide (4 g, 11.9 mmol) in DCM (60 cm^3) was added triethylamine (2.47 cm^3, 17.8 mmol) and the resulting solution was stirred at room temperature under nitrogen for 24 h. Concentration *in vacuo* to a crusty yellow oil and purification by flash column chromatography (SiO_2; Et_2O–hexane, 1 : 9 to 2 : 4 gradient elution) gave the *title compound* **8** (3.94 g, 8.9 mmol, 75%) as a colourless glassy oil (Found: C, 75.9; H, 6.7; N, 3.1. $C_{28}H_{29}NO_4$ requires C, 75.82; H, 6.59; N, 3.16%); $[\alpha]_D^{25}$ +23.5 ($c = 0.65$, DCM); ν_{max}(DCM)/cm^{-1} 3416w (NH), 1720s (C=O ester and carbamate) and 1506m [NHC(O)]; δ_H(300.0 MHz, $CDCl_3$) 1.41 [9 H, s, $C(CH_3)_3$], 3.09 (2 H, m, CH_2Ph), 4.20 (1 H, br t, *J* 7, $COOCH_2CH$), 4.29 (1 H, dd, *J* 7, 11, $COOCHH$), 4.44 (1 H, dd, *J* 7, 11, $COOCHH$), 4.55 (1 H, m, $NCHCO_2$), 5.28 (1 H, br d, *J* 8, NH) and 7.14–7.77 (13 H, m, H-2, H-3, H-4, H-5, H-6, H-9, H-10, H-11, H-12, H-15, H-16, H-17 and H-18); $\delta_C\{^1H\}$(75.5 MHz, $CDCl_3$) 26.7 [$C(CH_3)_3$], 37.2 (CH_2Ph), 45.9 (C-7), 53.8 ($NHCHCO_2$), 65.6 (CO_2CH_2), 81.2 [$C(CH_3)_3$], 118.7 (C-12 and C-15), 123.8 and 123.9 (C-9, C-10, C-17 and C-18), 125.7, 126.4, 127.2 and 128.3 (C-2, C-3, C-4, C-5, C-6, C-11 and C-16), 134.8 (C-1), 140.0 (C-13 and C-14), 142.9 (C-8 and C-19), 157.2 ($NHCO_2$) and 168.9 ($NCHCO_2$); *m*/*z* (CI, NH_3) 443 (M^+, 37%), 388 (M − C_4H_8, 3), 222 (H-Phe-O*t*BuH, 100), 179 ($C_{14}H_{11}$, 30) and 166 ($C_{13}H_{10}$, 56).

(*S*)-Tricarbonyl[*N*-(fluoren-9-ylmethoxycarbonyl)-η⁶-phenylalanine *tert*-butyl ester]chromium(0) 9

Fmoc-Phe-O*t*Bu **8** (2 g, 4.51 mmol), hexacarbonylchromium(0) (1.04 g, 4.74 mmol), anhydrous dibutyl ether (40 cm^3) and anhydrous THF (10 cm^3) were combined, and the mixture was thoroughly deoxygenated and heated to reflux under nitrogen for 40 h. The resulting red solution was cooled to ambient temperature and the solvent was evaporated at reduced pressure. Column chromatography (SiO_2; hexane–Et_2O 49 : 1 to 0 : 1 gradient elution) effected purification of the following products.

(i) Tricarbonyl(η⁶-dibenzofulvene)chromium(0) 10 (hexane–Et_2O 19 : 1). As a red solid (225 mg, 0.72 mmol, 16%), mp 135 °C dec. [Found: *m*/*z* (M) 314.0037, $C_{17}CrH_{10}O_3$ requires 314.0035]; ν_{max}(Et_2O)/cm^{-1} 1969vs, 1904s [Cr(C≡O)$_3$]; δ_H(300.0 MHz, $CDCl_3$) 5.41 (1 H, t, *J* 6, H-3 or H-4), 5.52 (1 H, t, *J* 6, H-3 or H-4), 5.93 (1 H, s, C*H*H), 5.97 (1 H, d, *J* 6, H-2 or H-5), 6.08 (1 H, s, CH*H*), 6.11 (1 H, d, *J* 6, H-2 or H-5), 7.36–7.41 (2 H, m, H-9 and H-10), 7.53–7.55 (1 H, m, H-8 or H-11) and 7.66–6.68 (1 H, m, H-8 or H-11); $\delta_C\{^1H\}$(90.6 MHz, $CDCl_3$) 85.3, 87.4, 90.1 and 91.7 (C-2, C-3, C-4 and C-5), 104.0 and 108.4 (C-1 and C-6), 108.5 (C=CH_2), 120.2, 121.3, 128.9 and 129.3 (C-8, C-9, C-10 and C-11), 127.6 (*C*=CH_2), 137.5 and 141.8 (C-7 and C-12) and 233.2 [Cr(CO)$_3$]; *m*/*z* (FAB positive) 314 (M^+, 65%), 286 (M − CO, 23), 258 (M − 2CO, 68), 230 (M − 3CO, 31), 178 (M − Cr − 3CO, 36) and 121 (M − Cr − 3CO − C_4H_9, 100).

(ii) Fmoc-Phe-O*t*Bu 8 (hexane–Et_2O 19 : 1 to 4 : 1). As a yellow stained oil (340 mg, 0.77 mmol, 17%).

(iii) Title complex 9 (hexane–Et_2O 0 : 1). As a solid yellow foam (820 mg, 1.42 mmol, 31%), mp 82–84 °C (Found: C, 64.1; H, 5.0; N, 2.2. $C_{31}H_{29}CrNO_7$ requires C, 64.24; H, 5.04; N, 2.42%); $[\alpha]_D^{20}$ +16.9 ($c = 1.0$, DCM); ν_{max}(DCM)/cm^{-1} 1969vs, 1892vs [Cr(C≡O)$_3$], 1723br (C=O ester and carbamate) and 1504m [NH(CO)]; δ_H(300.0 MHz, $CDCl_3$) 1.46 [9 H, s, $C(CH_3)_3$], 2.65 (1 H, dd, *J* 6, 14, C*H*HPh), 2.81 (1 H, dd, *J* 5, 14, CH*H*Ph), 4.18 (1 H, br t, *J* 7, $COOCH_2CH$), 4.33–4.44 (2 H, m, $COOCH_2$), 4.58 (1 H, m, $NCHCO_2$), 4.92 (1 H, d, *J* 6, NH), 5.09–5.41 (5 H, m, H-2, H-3, H-4, H-5 and H-6) and 7.30–7.79 (8 H, m, H-9, H-10, H-11, H-12, H-15, H-16, H-17 and H-18); $\delta_C\{^1H\}$(90.6 MHz, $CDCl_3$) 28.1 [$C(CH_3)_3$], 38.3 ($PhCH_2$), 47.3 (C-7), 55.2 ($NHCHCO_2$), 66.6 (CO_2CH_2), 83.5 [$C(CH_3)_3$], 90.7, 92.9, 93.4, 93.4 and 93.7 (C-2, C-3, C-4, C-5 and C-6), 107.0 (C-1), 120.0 and 120.1 (C-12 and C-15), 124.9, 125.1, 127.2, 127.9, 127.9 and 128.6 (C-9, C-10, C-11, C-16, C-17 and C-18), 141.4 (C-13 and C-14), 143.6 and 143.8 (C-8 and C-19), 155.4 ($NHCO_2$), 169.7 ($NCHCO_2$) and 232.7 [Cr(CO)$_3$]; *m*/*z* (FAB positive) 579 (M^+, 1.4%), 524 (MH − 2CO, 2.6), 495 (M − 3CO, 33), 439 [MH − 3CO − $C(CH_3)_3$, 8], 179 (dibenzofulveneH, 30), 147 ($PhCH_2CHNH_2$, 28), 91 ($PhCH_2$, 49) and 73 [$OC(CH_3)_3$, 100].

(*S*)-Dicarbonyl[*N*-(fluoren-9-ylmethoxycarbonyl)-η⁶-phenylalanine *tert*-butyl ester](polymer-bound triphenylphosphine)-chromium(0) 11

To a suspension of polymer-bound triphenylphosphine (450 mg, 0.72 mmolP) at ambient temperature in anhydrous THF (200 cm^3) left under constant nitrogen agitation for 20 min was added tricarbonyl(Fmoc-Phe-O*t*Bu)chromium(0) **9** (500 mg, 0.86 mmol) and the yellow mixture was subjected to periodic irradiation (4 × 10 min) over a 48 h period. The resulting deep red beads were filtered, washed thoroughly with alternate aliquots of THF and Et_2O and dried *in vacuo* to afford the *title resin* (732 mg, 0.69 mmol[Fmoc-Phe-O*t*Bu] g^{-1}); ν_{max}(Nujol)/cm^{-1} 2061vw and 1936w [polymer–$PPh_2Cr(C{\equiv}O)_5$], 2005w [polymer–$(PPh_2)_2Cr(C{\equiv}O)_4$], 1874vs and 1828s [polymer–$PPh_2Cr(C{\equiv}O)_2(Ar)$] and 1718m [C(=O)O*t*Bu]; $\delta_P\{^1H\}$(202.4 MHz, THF-swollen resin, D_2O capillary lock) −3.3 (10%, polymer–PPh_2), 27.4 [15, polymer–$P(O)Ph_2$], 58.0 [trace, polymer–$PPh_2Cr(CO)_5$], 78.4 [5, polymer–$(PPh_2)_2Cr(CO)_4$] and 93.2 [70, polymer–$PPh_2Cr(CO)_2$(Fmoc-Phe-O*t*Bu)]; *m*/*z* (FAB positive) 444 (Fmoc-Phe-O*t*BuH$^+$, 2%), 388 (Fmoc-Phe-OH + H, 5), 289 [$Ph_2P(C_6H_4)CHCH_2$, 17], 178 (dibenzofulvene, 29), 136 [Cr(CO)$_3$, 100], 120 (Phe − CO_2H, 23), 107 [$P(C_6H_4)$, 35] and 91 (C_7H_7, 24). Characterisation of the resin species was aided by comparison of the resin ^{31}P NMR and IR spectra with those of dicarbonyl(triphenylphosphine)(η⁶-toluene)chromium(0),[7] *trans*-tetracarbonylbis(triphenylphosphine)chromium(0)[16] and pentacarbonyl(triphenylphosphine)-chromium(0).[8]

(*S*)-Dicarbonyl(η⁶-phenylalanine *tert*-butyl ester)(polymer-bound triphenylphosphine)chromium(0) 12

To a suspension of dicarbonyl(Fmoc-Phe-O*t*Bu)(polymer–PPh_2)chromium(0) **11** (250 mg, 0.17 mmol[Fmoc-Phe-O*t*Bu]) in anhydrous DCM (8 cm^3) at ambient temperature was added piperidine (2 cm^3). After 20 mins under constant nitrogen agitation, the beads were filtered and washed with alternate aliquots of DCM and Et_2O. The process was repeated: re-suspension in 20% piperidine–DCM (10 cm^3) for 10 mins, filtration and washing as before afforded red beads of the *title compound resin*, taken directly to the next coupling step; ν_{max}(Nujol)/cm^{-1} 2061vw and 1936w [polymer–$PPh_2Cr(C{\equiv}O)_5$], 2005w [polymer–$(PPh_2)_2Cr(C{\equiv}O)_4$], 1883vs and 1832s [polymer–$PPh_2Cr(C{\equiv}O)_2(Ar)$] and 1720m [C(=O)O*t*Bu].

(*S*)-(η⁶-*N*-Acetylphenylalanine *tert*-butyl ester)dicarbonyl-(polymer-bound triphenylphosphine)chromium(0) 13

To a suspension of dicarbonyl(H-Phe-O*t*Bu)(polymer–PPh_2)chromium(0) **12** [derived from dicarbonyl(Fmoc-Phe-O*t*Bu)(polymer–PPh_2)chromium(0) **11** (250 mg, 0.17 mmol-[Fmoc-Phe-O*t*Bu]) as described above] in anhydrous DCM (8 cm^3) at ambient temperature was added first triethylamine (2 cm^3) then acetic anhydride (1 cm^3) and the mixture was left under constant nitrogen agitation for 3 h. The resulting red beads were filtered, washed thoroughly with alternate aliquots of DCM and Et_2O and dried *in vacuo* to afford the *title resin*

13 (230 mg, 0.71 mmol[Ac-Phe-O*t*Bu] g^{-1}); ν_{max}(Nujol)/cm^{-1} 2061vw and 1936w [polymer–$PPh_2Cr(C{\equiv}O)_5$], 2005w [polymer–$(PPh_2)_2Cr(C{\equiv}O)_4$], 1883vs and 1831s [polymer–$PPh_2Cr(C{\equiv}O)_2$(Ar)], 1727m [C(=O)O*t*Bu] and 1677m [C(=O)N]; $\delta_P\{^1H\}$(202.4 MHz, THF-swollen resin, D_2O capillary lock) −6.2 (10%, polymer–PPh_2), 24.7 [20, polymer–$P(O)Ph_2$], 56.3 [5, polymer–$PPh_2Cr(CO)_5$], 73.6 [5, polymer–$(PPh_2)_2Cr(CO)_4$] and 90.1 [60, polymer–$PPh_2Cr(CO)_2$(Ac-Phe-O*t*Bu)].

(*S*)-*N*-Acetylphenylalanine *tert*-butyl ester (Ac-Phe-O*t*Bu) 14[9]

Dicarbonyl(Ac-Phe-O*t*Bu)(polymer–PPh_2)chromium(0) **13** (90 mg, 0.064 mmol [Ac-Phe-O*t*Bu]) was ground to a fine yellow powder with a pestle and mortar, and suspended in DCM (30 cm^3) in a 50 cm^3 round-bottomed flask equipped with a condenser and $CaCl_2$ drying tube and was stirred at ambient temperature in air under white light (100 W) for 48 h. The resulting brown suspension was filtered through Celite and the polymeric residue was washed with DCM. The combined filtrate and washings were concentrated *in vacuo* and purified by flash column chromatography (SiO_2; DCM–hexane 0 : 1 to 1 : 4 gradient elution) to afford the colourless title compound **14** (13 mg, 0.049 mmol, 77%), $[\alpha]_D^{25}$ +58.2 (c = 1.0, $CHCl_3$) [lit.[16] $[\alpha]_D^{20}$ +60 (c = 1.0, $CHCl_3$)]; ν_{max}(neat)/cm^{-1} 3300br (NH), 1734vs (C=O ester), 1653vs (C=O amide) and 1540s [NHC(O)]; δ_H(360.0 MHz, $CDCl_3$) 1.41 [9 H, s, $C(CH_3)_3$], 1.99 [3 H, s, $C(O)CH_3$], 3.06–3.12 (2 H, m, $PhCH_2$), 4.73–4.79 (1 H, m, $NCHCO_2$), 5.92 (1 H, d, *J* 8, NH) and 7.13–7.31 (5 H, m, Ar-H); $\delta_C\{^1H\}$(90.6 MHz, $CDCl_3$) 23.3 [C(O)*C*H_3], 28.0 [$C(CH_3)_3$], 38.1 (Ph*C*H_2), 53.5 (N*C*HCO_2), 82.5 [*C*$(CH_3)_3$], 127.0 (C_{para}), 128.4 and 129.6 (C_{meta} and C_{ortho}), 136.2 (C_{ipso}), 169.5 and 170.9 ($NHCO_2$ and NCH*C*O_2).

(*S,S*)-Dicarbonyl[*N*-(fluoren-9-ylmethoxycarbonyl)valine-η⁶-phenylalanine *tert*-butyl ester](polymer-bound triphenylphosphine)chromium(0) 15

A solution of diisopropylethylamine (0.152 cm^3, 0.87 mmol) and Fmoc-Val-OH (148 mg, 0.44 mmol) in anhydrous DCM (2 cm^3) was added to a suspension of dicarbonyl(H-Phe-O*t*Bu)(polymer–PPh_2)chromium(0) **12** (derived from resin **11**, 250 mg, 0.17 mmol [Fmoc-Phe-O*t*Bu]) in anhydrous DCM (2 cm^3) at ambient temperature. PyBOP (227 mg, 0.44 mmol) was added immediately and the mixture was left under constant nitrogen agitation for 6 h. The resulting red beads were filtered, washed thoroughly with alternate aliquots of DCM, methanol and Et_2O and dried *in vacuo* to afford the *title resin* **15** (265 mg, 0.60 mmol[Fmoc-Val-Phe-O*t*Bu] g^{-1}); ν_{max}(Nujol)/cm^{-1} 2061vw and 1936w [polymer–$PPh_2Cr(C{\equiv}O)_5$], 2005w [polymer–$(PPh_2)_2Cr(C{\equiv}O)_4$], 1883vs and 1832s [polymer–$PPh_2Cr(C{\equiv}O)_2$(Ar)], 1724m [C(=O)O*t*Bu and OC(=O)N] and 1680m [C(=O)N] and 1494m [NHC(O)]; $\delta_P\{^1H\}$(202.4 MHz, THF-swollen resin, D_2O capillary lock) −4.8 (10%, polymer–PPh_2,), 26.2 [20, polymer–$P(O)Ph_2$], 57.8 [trace, polymer–$PPh_2Cr(CO)_5$], 75.1 [5, polymer–$(PPh_2)_2Cr(CO)_4$] and 91.8 [65, polymer–$PPh_2Cr(CO)_2$(Fmoc-Val-Phe-O*t*Bu)]; *m*/*z* (FAB positive) 543 (Fmoc-Val-Phe-O*t*BuH^+, 4%), 487 (Fmoc-Val-Phe-OH + H, 10), 289 [$Ph_2P(C_6H_4)CH{=}CH_2$, 19], 179 (dibenzofulvene + H, 56), 136 [$Cr(CO)_3$, 100], 120 (Phe − CO_2H, 28), 107 [$P(C_6H_4)$, 36] and 91 (C_7H_7, 39).

Fmoc-Val-Phe-O*t*Bu 16

Dicarbonyl(Fmoc-Val-Phe-O*t*Bu)(polymer–PPh_2)chromium(0) **15** (100 mg, 0.06 mmol [Fmoc-Val-Phe-O*t*Bu]) was ground to a fine yellow powder and suspended in DCM (15 cm^3) in a 25 cm^3 round-bottomed flask equipped with a condenser and $CaCl_2$ drying tube and stirred at ambient temperature in air under white light (100 W) for 48 h. The resulting fine brown suspension was filtered through Celite and the polymeric residue was washed with DCM. The combined filtrate and washings were concentrated at reduced pressure to afford the colourless *title dipeptide* (29 mg, 0.054 mmol, 90%); the optical rotation, IR, ^1H, ^{13}C NMR and mass spectrum of **16** were in excellent agreement with data obtained from a sample of **16** obtained by solution phase coupling: mp 133–134 °C (Found: C, 73.2; H, 7.2; N, 5.3. $C_{33}H_{38}N_2O_5$ requires C, 73.04; H, 7.06; N, 5.16%), $[\alpha]_D^{25}$ +15.0 (c = 0.8, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1732vs (C=O ester), 1692vs (C=O amide), 1657vs (C=O carbamate) and 1538vs [NHC(O)]; δ_H(360.0 MHz, $CDCl_3$) 0.94 [6 H, m, CH-$(CH_3)_2$], 1.39 [9 H, s, $C(CH_3)_3$], 2.10 [1 H, m, $CH(CH_3)_2$], 3.08 (2 H, m, CH_2Ph), 4.06 (1 H, m, Val-αH), 4.23 (1 H, brt, *J* 7, OCH_2CH), 4.33 (1 H, dd, *J* 7, 10, OC*H*H), 4.46 (1 H, dd, *J* 7, 10, OCH*H*), 4.78 (1 H, m, Phe-αH), 5.51 (1 H, d, *J* 9, NH), 6.43 (1 H, d, *J* 8, NH) and 7.14–7.78 (13 H, m, H-2 to H-6, H-9 to H-12 and H-15 to H-18); $\delta_C\{^1H\}$(90.6 MHz, $CDCl_3$) 17.9 and 19.2 [$CH(CH_3)_2$], 28.0 [$C(CH_3)_3$], 31.4 [$CH(CH_3)_2$], 38.2 ($PhCH_2$), 47.2 (C-7), 53.7 (Phe-αC), 60.3 (Val-αC), 67.1 (CO_2CH_2), 82.5 [$C(CH_3)_3$], 120.0 (C-12 and C-15), 125.2, 125.2, 127.1, 127.1, 127.8, 128.5 and 129.5 (C-2 to C-6, C-9 to C-11 and C-16 to C-18), 136.0 (C- 1), 141.4 (C-13 and C-14), 143.9 (C-8 and C-19), 156.4 (NCOO) and 170.3 and 170.8 (Val NCO, Phe NCO); *m*/*z* (FAB positive) 543 (MH^+, 11%), 487 (Fmoc-Val-Phe-OH + H, 36), 265 (H-Phe-Val-OH + 2H, 22), 179 (dibenzofulvene + H, 100), 136 [$Cr(CO)_3$, 13] and 120 (Phe − CO_2H, 28).

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