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The synthesis and characterisation of heterosubstituted aminoferrocenes

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Abstract

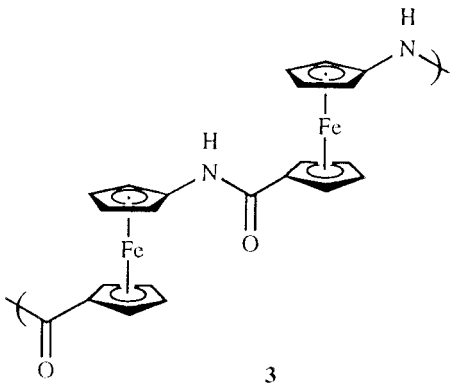
The synthesis of 1-bromo-1′-aminoferrocene is reported using a simple synthetic methodology. This compound serves as a useful precursor to other heterosubstituted aminoferrocenes. For example, (1′-amino)ferrocenecarboxylic acid has been obtained and is conveniently isolated in its *C*-protected form by lithiation of 1-bromo-1′-aminoferrocene, quenching with solid carbon dioxide and esterification of the resulting carboxylate with methanolic HCl. The new ligand 1-diphenylphosphino-1′-aminoferrocene has also been obtained using a similar methodology. © 1998 Elsevier Science S.A.

Keywords: Aminoferrocene; *C*-protected; Solid carbon dioxide

1. Introduction

The 1,1′-heterodisubstitution of ferrocene has received considerable attention recently with new synthetic methodology allowing the preparation of a number of useful synthetic precursors such as heterosubstituted aldehydes [1], halides [2], phosphines [3,4] and stannyl derivatives [5]. In several of these synthetic procedures 1-bromo-1′-lithioferrocene has been used as a key precursor [2,4,6]. This compound may be generated in situ from 1,1′-dibromoferrocene on treatment with *n*-butyllithium at −70°C, providing a convenient route to previously published ligands [7,8] such as those shown in Scheme 1. Moreover, our group has made extensive use of this reaction in the preparation of heterosubstituted phosphine ligands, particularly diferrocenes, (Scheme 2).

Our longstanding interest in this area of chemistry is aimed primarily at the preparation of compounds which should find use as catalysts or catalyst precursors, viz. phosphines and amines, and we therefore envisaged that a route to heterosubstituted aminoferrocenes might usefully start from 1-bromo-1′-aminoferrocene **1**. One target molecule of particular interest is the simple heterosubstituted aminoferrocene, (1′-amino)ferrocenecarboxylic acid **2**. In addition to being an interesting compound for coordination studies this molecule may be thought of as the monomer of the ferrocene-based polymer ferrolon,



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and it will undoubtedly be of interest in peptide synthesis as a non-natural amino acid (Plate 1).

Aminoferrocenes have been known for a considerable time and a number of synthetic routes are available for their synthesis, for example via lithiated [9,10] or phthalimido [11] intermediates, reduction of nitrofer-

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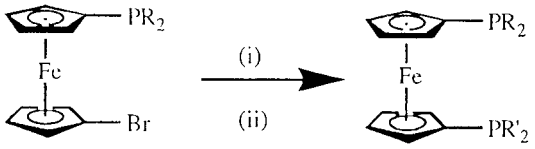


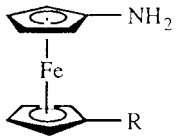
Scheme 1. Reagents: (i) ″BuLi (ii) $CIPR'_2$.

rocenes [12–14] diazines [15] and ferrocenylazides [11] or deprotection of acetylated amines [11].

2. Results and discussion

The methodology we chose to use was a modified version of the monolithiation of 1,1′-dibromoferrocene, recently published by Lai and Dong [2] and outlined above. The monolithiated intermediate was reacted with 0.4 equivalents of *O*-benzylhydroxylamine to yield 1-bromo-1′-aminoferrocene **1**, in yields of 45–55% based on the quenching reagent, as a pale yellow crystalline solid which may be stored at low temperature under an inert atmosphere. In common with other aminoferrocenes the compound decomposes to a black oil under ambient aerobic conditions over several hours. However, if nodules of sufficient size are obtained on crystallisation we have found that a protective coat is formed and we have had samples of this type exposed to air for several months without apparent decomposition. A small quantity (~14%) of the *n*-butyl-substituted amine byproduct, **4**, was also identified (by ^{1}H NMR and mass spectrometry) in the supernatant solution together with smaller quantities of the dibutyl-substituted amine product **5**, (6%) (Plate 2).

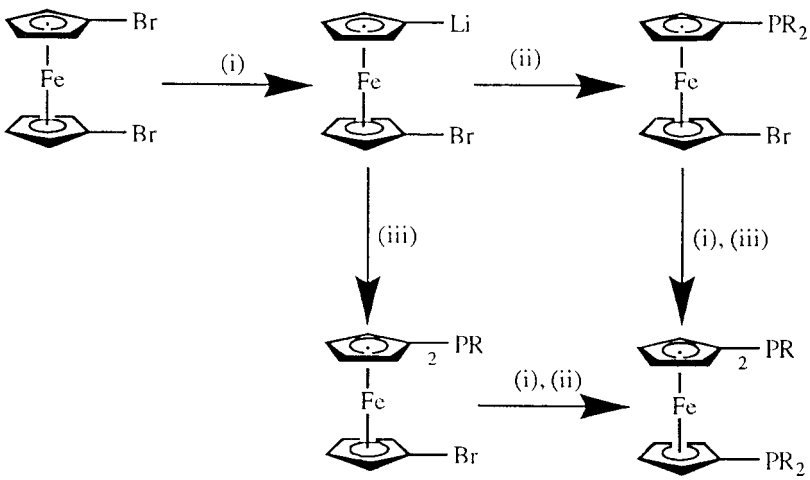
These may be separated by conventional column chromatography from compound **1** which is slower to elute than the alkyl-substituted byproducts. The byproducts are presumably formed as a consequence of the reaction of the lithiated amine with *n*-butyl bromide, which is formed in the initial exchange reaction. The small quantity of 1,1′-bis-(amino)ferrocene which is also obtained in the synthesis decomposes during work-up. The ^{1}H NMR spectra are characteristic, showing one ferrocenyl proton resonance, that of the protons *alpha* to the amino group, downfield of the other three. The relatively high yields of compound **1**



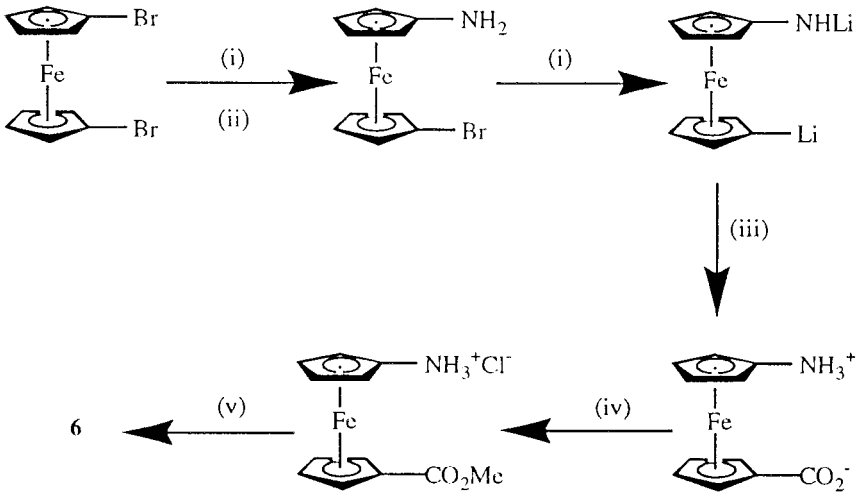
1 R = Br
2 R = CO_2H

in comparison to the similar literature preparation of aminoferrocene is the result of the slow addition of a limited amount of the quenching reagent. The main byproduct bromoferrocene, which was removed in a neutral fraction and isolated by column chromatography, serves as a useful synthon in its own right.

Lithiation of 1-bromo-1′-aminoferrocene was carried out using 2.5 equivalents of *n*-butyllithium. The use of dry solid carbon dioxide as a quenching reagent resulted in the immediate precipitation of amino acid **2** in the form of a water-soluble salt which was removed by filtration and washed with diethyl ether. The identity of the crude product was confirmed by NMR, however the salt was contaminated somewhat with butylated byproducts. Further evidence for the presence of the Zwitterionic salt was demonstrated by its inability to be extracted from aqueous solution under either acidic or basic conditions. Attempts at dissolution in water followed by organic solvent washing, evaporation and

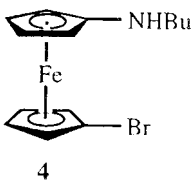


Scheme 2. Reagents: (i) ″BuLi (ii) $CIPR_2$ (iii) Cl_2PR'.



Scheme 3. Reagents: (i) ″BuLi (ii) $BnONH_2$ (iii) CO_2 (iv) AcCl/MeOH (v) NaOH.

extraction into dry methanol met with limited success. Finally a procedure was developed, using conventional organic synthetic techniques, which allowed for the isolation of the methyl ester by treatment of the crude solid initially obtained with methanolic hydrogen chloride. Rapid exothermic dissolution occurred and the mixture was stirred overnight before being treated with a dilute aqueous sodium hydroxide solution and extracted with diethyl ether. Three major products were then isolated by column chromatography, compounds **6**, **7** and **8**[1]



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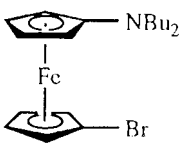

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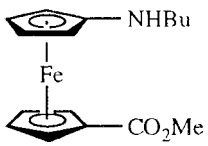
in the ratio 62:9:24, (Plate 3) (Scheme 3).

The major product **8** was obtained as deep orange crystals which were found to be considerably more stable than either of compounds **6**



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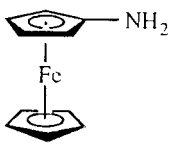
and **7**.



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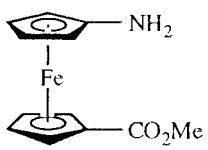

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Compound **8** may be considered as a useful latent source of the polymer **3**. Preliminary attempts at structural characterisation of compound **8** using X-ray crystallography have been unsuccessful due to twinning however it has been established that the compound crystallises as a hydrogen-bonded dimer. An alternative isolation procedure which involved chromatography of

[1] Compound **7** identified by spectral comparison with an authentic sample arises from the use of solid carbon dioxide which condensed traces of water during transfer.

an aqueous solution of the amino acid fraction using Sephadex resulted in the isolation of compound **2** as a buff coloured powder however it was found to be contaminated with small quantities of pentanoic acid which was formed as a byproduct from the reaction of residual butyllithium with carbon dioxide. Nevertheless it was possible to characterise compound **2** using NMR and mass spectrometry. The difficulty experienced in the isolation of the amino acid may in part be due to the formation of intermediate complexes in which the *N*-lithio function has also been trapped with carbon dioxide [15]. The reaction of 1-diphenylphosphino-1′-lithioferrocene prepared in situ from 1-bromo-1′-(diphenylphosphino)ferrocene with *O*-benzylhydroxylamine using a similar work-up procedure to that used in the preparation of compound **2** resulted in the formation of **1**-diphenylphosphino-1′-aminoferrocene, **9** which may be considered as the ferrocene equivalent of the well-known organic ligand 2-(diphenylphosphino)aniline. This compound was observed to darken on prolonged standing in air and thus may not be such a useful ligand for want of ease of handling. The ^{31}P NMR spectrum consists of a singlet at -17.57 ppm which is only slightly shifted downfield from that of (diphenylphosphino)ferrocene (-17.2 ppm). A preliminary investigation into the coordination behaviour of this ligand with palladium (II) resulted in the formation of the bidentate complex although the reaction was not clean, possibly due to the rapid coordination of the phosphorus and the slower coordination of the nitrogen which would give intermediate diligand complexes. Further coordination studies on this ligand will be reported in a subsequent communication (Plate 4).

Clearly the use of other quenching reagents will lead to the preparation of a wide range of aminoferrocenes, for example quenching with DMF gives rise to the anticipated (1′-amino)ferrocenecarbaldehyde and substituted derivatives [2] which are readily separable by column chromatography [16] and are obtained as orange air and light sensitive solids after purification. The initial derivatisation of compound **1** will allow for the synthesis of a wide range of heterosubstituted aminoferrocene derivatives such as azoferrocenes and ferrocenylisonitriles. The work is now focused on the preparation of polyferrocene derivatives from these precursors.

3. Summary

A convenient and rapid synthesis of heterosubstituted aminoferrocenes has been developed which allows for the preparation of simple yet important precursor compounds including the new ligand 1-diphenylphosphino-1′-aminoferrocene and substituted derivatives of (1′-amino)ferrocenecarboxylic acid.

4. Experimental

4.1. General

All experiments were run under a dry nitrogen atmosphere using standard Schlenk glassware. ^{1}H NMR spectra were recorded on a Bruker AC250 instrument operating at 250 MHz for ^{1}H. δ values are given in ppm and are relative to TMS as internal standard. J values are given in Hz. Mass spectra were recorded using a variety of techniques including electron impact, chemical ionization, FAB and electrospray at the EPSRC National Laboratory Service at the University of Wales, Swansea. Column chromatography was routinely performed using a neutral alumina support, Brockman Grade 1. All solvents were predried using conventional methods and were distilled prior to use. 1,1′-Dibromoferrocene was made by a modification of the literature procedure typically on a 50 g scale.

4.2. Preparation of 1-bromo-1′-aminoferrocene, *1*

A solution of 1,1′-dibromoferrocene (3.44 g, 10 mmol) in THF (25 ml) was cooled to -70°C in an external acetone/dry ice bath. To this solution was added *n*-butyllithium (4 ml of a 2.5 M sol. in hexane). The mixture was allowed to stir for 10 min. A solution of *O*-benzylhydroxylamine (0.49 g, 4 mmol) in THF (10 ml) was then added and the mixture was allowed to warm to ambient temperature with stirring over 1 h. The product was quenched with water (10 ml) before being extracted into 20 ml of dilute HCl. The aqueous layer was washed with diethyl ether (20 ml). Fresh ether (20 ml) was added and the mixture was slowly made basic with dil. sodium hydroxide. The yellow product transferred to the ether layer which was separated and a further extraction was performed with the same volume of ether. The combined organic fractions were dried over anhydrous magnesium sulfate and the solvent was removed in vacuo. Purification was achieved either by crystallisation of the product **1** from a minimum volume of hexane overnight at -10°C, (yield 0.8 g, 71%) or by column chromatography on a basic alumina support, which also afforded the faster eluting *n*-butyl-substituted aminoferrocene, **4** (14%) and small quantities of the dibutylated derivative **5** (6%). **1**: $C_{10}H_{10}BrFeN$: ^{1}H NMR ($CDCl_3$) $\delta = 2.71$ (bs, 2H), 3.94 (t, 2H, $J = 1.6$), 3.95 (t, 2H, $J = 1.6$), 4.05 (t, 2H, $J = 1.8$), 4.32 (t, 2H, $J = 1.8$). ^{1}H{^{13}C} NMR ($CDCl_3$) $\delta = 60.4$ (2 × CH), 63.7 (2 × CH), 67.3 (2 × CH), 70.7 (2 × CH), 79.3

[2] *N*-substitution is also observed.

(>C<), 106.4 (>C<). Mass spectrum *m/z* (rel. int.): 281 (45), 279 (47), 257 (100), 201 (81), 108 (26). **4**: $C_{14}H_{18}BrFeN$: ^1H NMR ($CDCl_3$) $\delta = 0.95$ (t, 3H, $J = 7.0$), 1.41 (pseudo sxt, 2H, $J = 7.0$), 1.55 (pseudo sxt, 2H, $J = 7.0$), 2.24 (bs, 1H), 2.92 (t, 2H, $J = 7.0$), 3.83 (t, 2H, $J = 1.8$), 3.90 (t, 2H, $J = 1.8$), 4.00 (t, 2H, $J = 1.9$), 4.32 (t, 2H, $J = 1.9$). $^1H\{^{13}C\}$ NMR ($CDCl_3$) $\delta = 14.1$ (CH_3), 20.5 (CH_2), 32.1 (CH_2), 46.7 (CH_2), 57.5 (2×CH), 65.3 (2×CH), 66.8 (2×CH), 70.1 (2×CH), 78.9 (>C<), 112.5 (>C<). Mass spectrum *m/z* (rel. int.): 337 (88), 335 (93), M^+, 257 (100). **5**: $C_{18}H_{26}BrFeN$: ^1H NMR ($CDCl_3$) $\delta = 0.94$ (t, 6H, $J = 7.0$), 1.34 (pseudo sxt, 4H, $J = 7.0$), 1.56 (pseudo sxt, 4H, $J = 7.0$), 2.92 (t, 4H, $J = 7.0$), 3.67 (t, 2H, $J = 1.8$), 3.94 (t, 2H, $J = 1.8$), 4.03 (t, 2H, $J = 1.9$), 4.32 (t, 2H, $J = 1.9$). Mass spectrum *m/z*: 393 (98), 391 (100), $M^{+\cdot}$.

4.3. Preparation of (1′-amino)ferrocenecarboxylic acid, *2*

1-Bromo-1′-aminoferrocene **1** (2.8 g, 10 mmol) in diethyl ether (30 ml) was treated with 2.5 equivalents of *n*-butyllithium (10 ml of a 2.5 M sol. in hexane) at −70°C. The mixture was allowed to warm to −50°C over 10 min, darkening considerably, and was treated with excess dry carbon dioxide before being allowed to warm to ambient temperature. The resultant bright yellow-orange suspension was filtered and the residue was washed with ether (3×30 ml). Chromatography of this solid using Sephadex yielded a yellow-orange powder, **2**, contaminated with pentanoic acid which co-elutes. **2**: $C_9H_{11}FeNO_2$: ^1H NMR (D_2O) $\delta = 3.92$ (bm, 2H), 4.14 (bm, 2H), 4.40 (bm, 2H), 4.65 (bm, 2H). Mass spectrum (electrospray) 245 (8), 244 (100), $M^{+\cdot}$–H, 200 (22). Salt extract: ^1H NMR (D_2O, HOD suppressed) $\delta = 4.38$ (m, 2H), 4.21 (m, 2H), 4.02 (m, 2H), 3.98 (m, 2H). Mass spectrum (E.I.) *m/z*:378 (32), 334 (100), 290 (63), 275 (31), 262 (46), 226 (27), 218 (41), 177 (81), 157 (28), 134 (67).

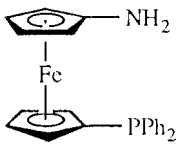
4.4. Preparation of methyl (1′-amino)ferrocenecarboxylate, *8*

1-Bromo-1′-aminoferrocene **1** (2.8 g, 10 mmol) in a mixture of diethyl ether and THF (50:50, 30 ml) was treated with 2.5 equivalents of *n*-butyllithium (10 ml of a 2.5 M sol. in hexane) at −70°C. The mixture was allowed to warm to −50°C over 10 min and was treated with excess dry carbon dioxide before being allowed to warm to ambient temperature. The mixture was then quenched with water (20 ml) and the aqueous product-containing fraction was separated and dried under vacuum to give a pale yellow powder. This product was then redissolved in methanol before being treated slowly with a solution of methanolic HCl (prepared by the careful addition of acetyl chloride to methanol). After stirring overnight the reaction mixture was brought to pH8 by the dropwise addition of dil. sodium hydroxide. The product mixture was extracted into diethyl ether (3×20 ml) and dried over magnesium sulfate and the solvent was removed in vacuo. Column chromatography on neutral alumina afforded compounds **6** (24%), **7** (9%) and the major product compound **8** (1.6 g, 62%) as a deep orange-red solid from the third orange band. **8**: $C_{10}H_{13}FeNO_2$: ^1H NMR ($CDCl_3$) $\delta = 1.59$ (bs, 2H), 3.81 (s, 3H), 3.88 (t, 2H, $J = 1.8$), 3.98 (t, 2H, $J = 1.8$), 4.35 (t, 2H, $J = 1.9$), 4.77 (t, 2H, $J = 1.9$). $^1H\{^{13}C\}$ NMR ($CDCl_3$) $\delta = 59.3$ (CH_3), 65.1 (2×CH), 65.8 (2×CH), 70.9 (2×CH), 71.7 (2×CH), 72.3 (>C<), 106.9 (>C<), 156.3 (>C<). Mass spectrum (E.I.) *m/z*: 259 (100), 228 (4), 167 (12), 143 (3), 137 (8). Accurate mass: 259.02731, $\Delta = 10$ ppm. **6**: $C_{14}H_{21}FeNO_2$: ^1H NMR ($CDCl_3$) $\delta = 0.94$ (t, 3H, $J = 7.0$), 1.21 (m, 2H), 1.52 (m, 2H), 1.61 (bs, 1H), 2.94 (t, 2H, $J = 7.0$), 3.74 (s, 3H), 3.83 (t, 2H, $J = 1.8$), 3.86 (t, 2H, $J = 1.8$), 4.32 (t, 2H, $J = 1.9$), 4.72 (t, 2H, $J = 1.9$). $^1H\{^{13}C\}$ NMR ($CDCl_3$) $\delta = 13.9$ (CH_3), 20.4 (CH_2), 29.7 (CH_2), 32.0 (CH_2), 56.4 (2×CH), 64.7 (2×CH), 65.8 (2×CH), 70.2 (2×CH), 71.2 (>C<), 156.6 (>C<). Mass spectrum (E.I.) *m/z*: 315 (100), 284 (3), 259 (6), 240 (7), 223 (19), 189 (22). **7**: $C_{10}H_{11}FeN$: ^1H NMR ($CDCl_3$) $\delta = 2.54$ (bs, 2H), 3.89 (m, 2H), 3.96 (m, 2H), 4.07 (s, 5H); identified by spectral comparison with an authentic sample prepared by the direct water quenching of 1-amino-1′-lithioferrocene.

4.4.1. Preparation of 1-diphenylphosphino-1′-aminoferrocene, *9*

To a solution of 1-bromo-1′-(diphenylphosphino)ferrocene (4.49 g, 10 mmol) in THF (25 ml) at −10°C was added 1 equivalent of *n*-butyllithium (4 ml of a 2.5 M sol. in hexane) over 10 min., followed by a solution of *O*-benzylhydroxylamine (4.9 g, 4 mmol) in THF (10 ml). The mixture was allowed to warm to ambient temperature over 1 h. and was then quenched with water (20 ml). The product was extracted into dil. aqueous hydrochloric acid solution which was then separated from the organic layer. Diethyl ether was added and the product was liberated from the organic layer by the slow addition of dil. sodium hydroxide solution. Following drying over magnesium sulfate, the solvent was removed from the filtered solution which was then reduced to an oil under vacuum. The yellow product was dissolved in the minimum volume of hot hexane and allowed to cool and crystallise. Yield: (based on added amine, 0.59 g, (38%) **9**: $C_{22}H_{20}FeNP$: ^1H NMR ($CDCl_3$) $\delta = 2.30$ (bs, 2H), 3.74 (t, 2H, $J = 1.8$) 3.87 (t, 2H, $J = 1.8$), 3.98 (t, 2H, $J = 1.9$), 4.27 (t, 2H, $J = 1.9$), 7.15–7.45 (bm, 10H). Mass spectrum *m/z*: 385 (100), M^+. $^1H\{^{31}P\}$ NMR ($CDCl_3$) $\delta = -17.57$(s).

4.4.2. Preparation of a palladium complex of compound



A solution of the ligand **9** (0.5 g, 1.3 mmol) in dichloromethane (7 ml) was treated with a solution of $[Pd(COD)Cl_2]$ (0.38 g, 1.3 mmol) also in dichloromethane (7 ml). The solution changed colour from yellow to a deep red on addition. The product was precipitated from solution after 1 h. by the addition of diethyl ether, as a deep red powder. Attempted recrystallisation from biphasic dichloromethane/ether 1:1 gave only a powdered product. ($LPdCl_2$): ^1H NMR ($CDCl_3$) $\delta = 3.74$ (m, 2H), 4.00 (m, 2H), 4.21 (m, 2H), 4.41 (m, 2H), 7.14–7.50 (m, 6H), 7.50–7.80 (m, 4H). $^1H\{^{31}P\}$ NMR ($CDCl_3$) $\delta = +15.77$ (s). Mass spectrum (FAB): cluster centred at m/z 490 (100), M^+-2 Cl; 385 (60). (N.B. a weak cluster was also observed centred at m/z 596 which corresponds to LPd_2).

Acknowledgements

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