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Application of the chiral auxiliary $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)]$ to the stereoselective formation of 4-substituted-1,4-dihydronicotinoyl complexes

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Abstract

In solution regio- and stereoselective additions of nucleophiles to (*RS*)-$[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)CO\text{-}3\text{-pyridyl}]$ (**1**) occur at C-4 to give the corresponding nitrogen-stabilised anions. Subsequent quenching of these anions by a proton, a chloroformate or dimethyl sulfate gives the corresponding 1,4-dihydropyridine complexes as single diastereoisomers. The predicted stereochemical course of the nucleophilic additions is confirmed by a single crystal X-ray structure determination of (Fe-*RS*,4-*RS*)-$[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)]$CO-3-(*N*-methoxycarbonyl-4-methyl-1,4-dihydropyridyl)].

Keywords: Crystal structures; Iron complexes; Cyclopentadienyl complexes; Nicotinoyl complexes

1. Introduction

Chiral 4-substituted-1,4-dihydropyridines represent an important class of compounds not only because they are potent calcium channel blockers [1] but also because they may be utilised as models for the coenzyme NADH [2,3] and as intermediates in alkaloid synthesis [4]. Consequently the generation of 4-substituted-1,4-dihydropyridines by nucleophilic additions to the pyridine nucleus, and in particular the stereoselectivity of these additions, has been the subject of considerable synthetic interest [5–7]. It has been established that high regioselectivity for C-4 addition may be achieved either with copper reagents [5] or, if the substrate possesses a substituent capable of directing attack, with a wider range of nucleophiles [6,7]. Interestingly, Meyers and Oppenlaender recently demonstrated that if the directing substituent is a chiral oxazoline at C-3 then the stereoselective incorporation of a nucleophile at C-4 can be achieved in up to 90% enantiomeric excess [3]. As part of our continuing studies into the formation of NADH mimics capable of achieving highly stereoselective reductions the reactions of a nicotinoyl fragment attached to the chiral auxiliary $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)]$ [8] are being investigated. In this report we describe the highly stereoselective conversion of the nicotinoyl complex **1** [1], the preparation and some reactions of which have been previously communicated [8e,9] to a wide range of 4-substituted-1,4-dihydropyridine complexes. It has been previously shown that reductions carried out by some homochiral C-4 substituted NADH mimics can occur with high stereoselectivity [3,10].

2. Results

A detailed description of the synthesis of the racemic nicotinoyl complex **1** has been outlined previously [8e]. In summary, **1** may be readily prepared in two steps; addition of nicotinoyl chloride [11] to $[(\eta^5\text{-}C_5H_5)Fe(CO)_2]^-Na^+$ [12] gives the achiral complex $[(\eta^5\text{-}C_5H_5)Fe(CO)_2$-nicotinoyl] which undergoes photolytic ligand exchange of carbon monoxide for triphenylphosphine in cyclohexane to yield complex **1**. Fig. 1 shows the X-ray crystal structure of complex **1**. Final atomic positional coordinates are listed in Table 1 and selected bond lengths and bond angles are given in Table 2. In common with other $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)]$ acyl complexes [13], the geometry around iron is

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[1] All complexes are racemic but only those with the (*R*)-configuration are shown for clarity.

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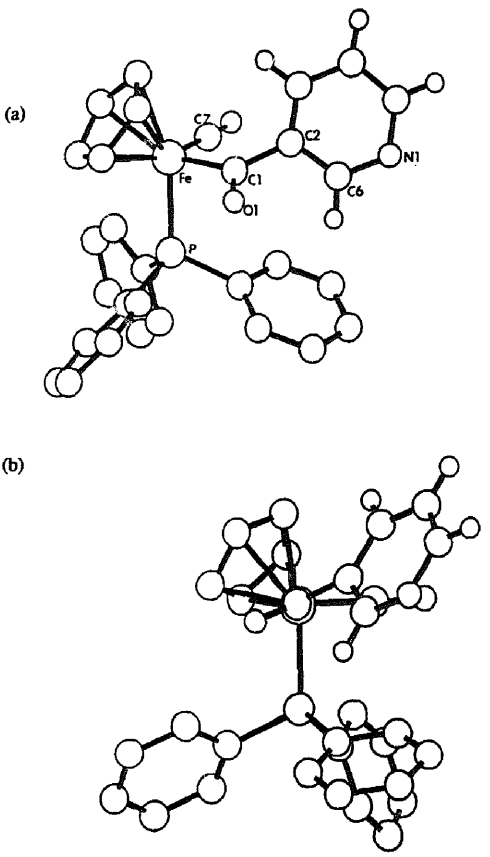


Fig. 1. The molecular structure of complex **1** as determined by X-ray crystallography showing the crystallographic numbering. Selected hydrogen atoms have been removed for clarity. Projections (a) from O1–C1 and (b) from Cl–Fe are illustrated.

close to octahedral [14] and the acyl oxygen is *anti* to the CO ligand. The nicotinoyl C-4 is *transoid* with respect to the acyl oxygen with the torsion angle between C=O and C-3–C-4 being −135°.

Treatment of complex **1** with alkyl or aryllithium reagents (RLi) in tetrahydrofuran at −78°C results in exclusive attack at the 4-position to generate the corresponding anions **2a–c** (R = CH_3 (**a**), Ph (**b**), ^{n}Bu (**c**)) (Scheme 1). This reaction was slower with methyllithium (10 equiv.) than with phenyl or n-butyllithium (1.5 equiv.) and Grignard reagents do not appear to react at all. Subsequent quenching of the anions **2a–c** with methanol generates the respective 4-substituted complexes **3a–c** as single diastereoisomers. ^{1}H (300 MHz) and ^{31}P (101.26 MHz) NMR spectroscopy showed **3a–c** to be in each case the only product, aside from small quantities of unreacted starting material. The chemical shifts and coupling constants of the three olefinic protons are characteristic of a 1,4-dihydropyridine [15], indicating the introduction of a substituent at the 4-position of **1**. The proton at the 4-position of the resulting 1,4-dihydropyridine is shifted upfield in each case (0.75–1.5 ppm), in comparison with similarly substituted 1,4-dihydropyridines [2,3,15], suggesting that it is proximate to and thus shielded [16] by one of the phenyl rings of the triphenylphosphine ligand.

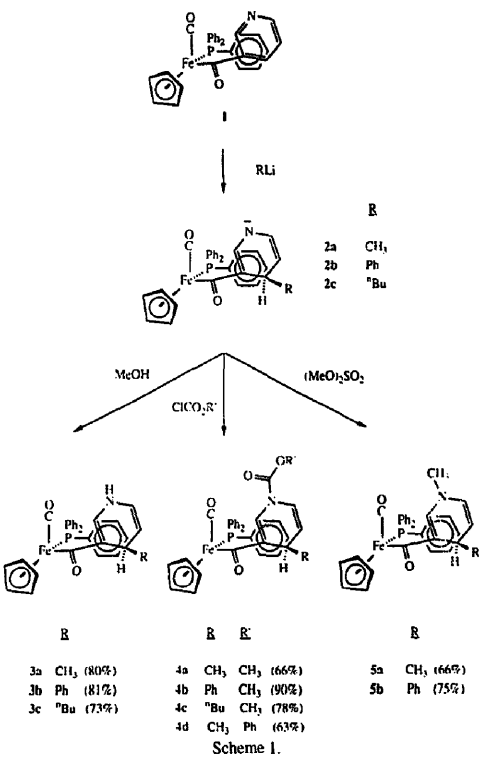
Quenching the anions **2a–c** with chloroformates ($ClCO_2R'$) gave the corresponding N-acylated 4-substituted-1,4-dihydropyridine complexes **4a–d** (Scheme 1). The

Table 1
Atomic coordinates for complex **1** with e.s.d.s in parentheses

Atom	*x/a*	*y/b*	*z/c*
Fe	0.20394(2)	0.15277(2)	0.13987(4)
P	0.32302(3)	0.14670(3)	0.28951(6)
O(1)	0.2493(1)	0.01259(9)	0.0469(2)
O(2)	0.1150(1)	0.1630(1)	0.4339(2)
N(1)	0.1177(2)	−0.1052(1)	0.3671(3)
C(1)	0.2019(1)	0.0473(1)	0.1252(3)
C(2)	0.1399(1)	0.0025(1)	0.2091(3)
C(3)	0.0580(2)	0.0196(2)	0.2064(4)
C(4)	0.0059(2)	−0.0272(2)	0.2819(5)
C(5)	0.0390(3)	−0.0879(2)	0.3591(4)
C(6)	0.1665(2)	−0.0605(1)	0.2912(3)
C(7)	0.1511(1)	0.1566(1)	0.3180(3)
C(8)	0.1625(2)	0.1517(2)	−0.1166(3)
C(9)	0.2402(2)	0.1828(2)	−0.0973(3)
C(10)	0.2361(2)	0.2452(1)	0.0020(3)
C(11)	0.1552(2)	0.2519(2)	0.0439(4)
C(12)	0.1094(2)	0.1929(2)	−0.0279(4)
C(13)	0.3372(1)	0.0657(1)	0.4206(3)
C(14)	0.2882(2)	0.0579(1)	0.5522(3)
C(15)	0.2939(2)	−0.0032(2)	0.6529(3)
C(16)	0.3484(2)	−0.0571(1)	−0.6219(4)
C(17)	*0.3970(2)*	*−0.0500(1)*	*0.4930(4)*
C(18)	0.3921(2)	0.0108(1)	0.3921(4)
C(19)	0.4137(1)	0.1479(1)	0.1697(3)
C(20)	0.4185(2)	0.0981(1)	0.0399(3)
C(21)	0.4866(2)	0.0963(1)	−0.0507(3)
C(22)	0.5504(2)	0.1443(2)	−0.0155(3)
C(23)	0.5456(2)	0.1949(2)	0.1094(3)
C(24)	0.4774(2)	0.1973(1)	0.2014(3)
C(25)	0.3430(1)	0.2178(1)	0.4477(3)
C(26)	0.2966(2)	0.2809(1)	0.4402(3)
C(27)	0.3105(2)	0.3344(1)	0.5600(3)
C(28)	0.3703(2)	0.3251(1)	0.6901(3)
C(29)	0.4162(2)	0.2630(1)	0.7005(3)
C(30)	0.4025(2)	0.2093(1)	0.5807(3)

Table 2
Selected bond lengths (Å) and angles (°) for complex **1**

Fe–P	2.2032(6)	C(7)–Fe–P	91.31(8)
Fe–C(1)	1.954(2)	C(7)–Fe–C(1)	94.3(1)
Fe–C(7)	1.734(2)	O(1)–C(1)–Fe(1)	123.2(2)
C(1)–O(1)	1.222(3)	C(2)–C(1)–O(1)	114.9(2)
C(1)–C(2)	1.511(3)	C(6)–C(2)–C(1)	118.4(2)
C(2)–C(6)	1.391(4)	C(2)–C(6)–N(1)	124.2(3)
C(6)–N(1)	1.332(3)	C(6)–N(1)–C(5)	116.4(3)
N(1)–C(5)	1.322(5)	C(4)–C(5)–N(1)	124.5(3)
C(5)–C(4)	1.372(5)	C(5)–C(4)–C(3)	118.3(3)
C(4)–C(3)	1.389(4)	C(4)–C(3)–C(2)	118.9(3)
C(3)–C(2)	1.375(4)		



Scheme 1.

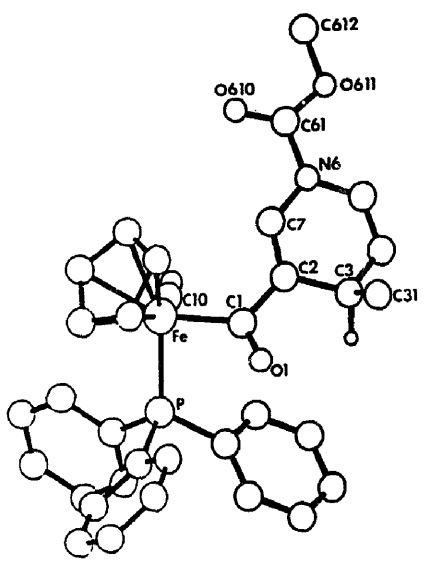


Fig. 2. The molecular structure of complex **4a** as determined by X-ray crystallography showing the crystallographic numbering. All hydrogens except that at C-4 have been omitted for clarity.

^{1}H NMR (300 MHz) spectra of complexes **4a–d** in deuteriochloroform are complex due to restricted rotation about the amide bond. Satisfactory spectra were obtained in dimethyl sulfoxide-d^6 at 333 K and were consistent in each case with formation of a single regio- and diastereomer. The structure and relative stereochemistry within complex **4a** was established by X-ray crystal structure analysis. Fig. 2 shows the X-ray crystal structure of complex **4a** with the final atomic positional coordinates listed in Table 3 and selected bond lengths and bond angles given in Table 4.

Attempts to quench the intermediate anions **2a–c** with less reactive electrophiles such as methyl iodide and benzyl bromide gave rise to complicated product mixtures from which the desired N-alkylated 4-substituted-1,4-dihydropyridine complexes could not be isolated. However, the anions **2a** and **2b** do react with dimethyl sulfate to give the corresponding N-methyl 4-substituted-1,4-dihydropyridine complexes **5a**

Table 3
Atomic coordinates for complex **4a**

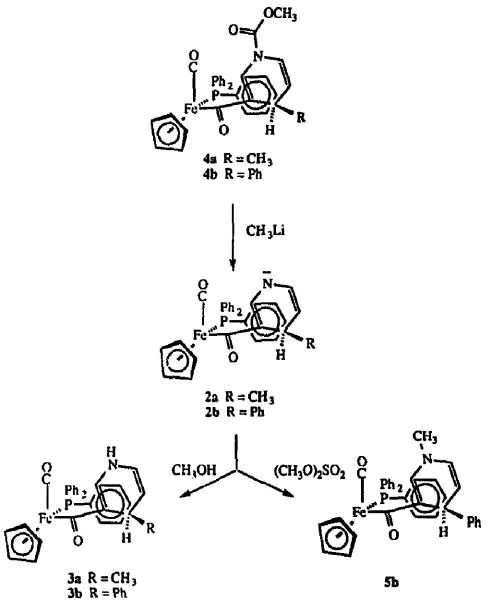
Atom	*x/a*	*y/b*	*z/c*
Fe	0.1785(2)	0.1165(2)	0.6094(2)
P	0.3046(5)	0.1054(3)	0.7443(4)
C(10)	0.2220(19)	0.0327(13)	0.5499(15)
O(10)	0.2454(14)	−0.0246(8)	0.5432(11)
C(1)	0.2941(18)	0.1762(12)	0.5521(16)
O(1)	0.3402(14)	0.2277(8)	0.5931(12)
C(2)	0.3219(19)	0.1575(13)	0.4536(16)
C(3)	0.4372(19)	0.1865(14)	0.4253(17)
C(4)	0.4653(19)	0.1474(15)	0.3364(20)
C(5)	0.3869(24)	0.1122(17)	0.2748(19)
N(6)	0.2732(18)	0.0999(11)	0.2932(14)
C(7)	0.2523(19)	0.1196(14)	0.3848(17)
C(31)	0.4373(19)	0.2705(13)	0.4098(18)
C(61)	0.1901(27)	0.0625(15)	0.2301(18)
O(610)	0.0982(17)	0.0484(10)	0.2535(12)
O(611)	0.2248(18)	0.0435(12)	0.1469(13)
C(612)	0.1431(32)	0.0036(20)	0.0819(25)
C(11)	0.0016(10)	0.0861(6)	0.6123(10)
C(12)	0.0364	0.1381	0.6872
C(13)	0.0698	0.2030	0.6426
C(14)	0.0556	0.1911	0.5401
C(15)	0.0134	0.1189	0.5214
C(101)	0.4574(9)	0.1133(8)	0.7333(11)
C(102)	0.5299	0.1630	0.7895
C(103)	0.6454	0.1693	0.7765
C(104)	0.6888	0.1261	0.7073
C(105)	0.6163	0.0764	0.6511
C(106)	0.5007	0.0701	0.6641
C(201)	0.3021(11)	0.0171(5)	0.8078(9)
C(202)	0.1984	−0.0218	0.7994
C(203)	0.1936	−0.0878	0.8492
C(204)	0.2925	−0.1148	0.9075
C(205)	0.3962	−0.0758	0.9159
C(206)	0.4010	−0.0099	0.8660
C(301)	0.2883(10)	0.1729(7)	0.8403(9)
C(302)	0.2884	0.2464	0.8130
C(303)	0.2759	0.3008	0.8811
C(304)	0.2625	0.2819	0.9766
C(305)	0.2634	0.2085	1.0039
C(306)	0.2759	0.1540	0.9357

Table 4
Selected bond lengths (Å) and angles (°) for complex **4a**

Fe–P	2.206(6)	C(1)–Fe–P	88.8(6)
Fe–C(1)	1.993(23)	C(10)–Fe–P	89.8(7)
Fe–C(10)	1.730(24)	C(10)–Fe–C(1)	96.4(10)
C(1)–O(1)	1.185(26)	O(1)–C(1)–Fe	122.1(18)
C(1)–C(2)	1.489(33)	C(7)–C(2)–C(1)	125.0(21)
C(2)–C(7)	1.346(31)	C(3)–C(2)–C(1)	118.1(18)
C(7)–N(6)	1.376(32)	C(2)–C(7)–N(6)	128.0(22)
N(6)–C(5)	1.408(36)	C(7)–N(6)–C(5)	115.3(19)
C(5)–C(4)	1.320(36)	N(6)–C(5)–C(4)	122.9(26)
C(4)–C(3)	1.503(37)	C(5)–C(4)–C(3)	123.0(23)
C(3)–C(2)	1.551(34)	C(4)–C(3)–C(2)	110.5(19)
C(3)–C(31)	1.552(35)	C(4)–C(3)–C(31)	110.7(21)
N(6)–C(61)	1.385(33)	N(6)–C(61)–O(601)	120.5(24)
		C(61)–O(611)–C(612)	115.1(25)

and **5b**, respectively, as single diastereoisomers in each case (Scheme 1).

Treatment of **4a** or **4b** with methyllithium (4.4 equiv.) followed by methanol gave **3a** and **3b**, respectively, in near quantitative yield (Scheme 2). In the latter case when methanol was replaced by dimethyl sulfate the *N*-methyl 4-phenyl-1,4-dihydropyridine complex (**5b**) was isolated in 94% yield. This illustrates that regeneration of the nitrogen-stabilised anions **2** directly from complexes **4** is possible, allowing the conversion of the latter to complexes **3** and **5**.



Scheme 2.

3. Discussion

Although the X-ray crystal structure of **1** shows the nicotinoyl 4-position is *transoid* with respect to the acyl oxygen, the crystal structure of the analogous compound, [(η^5-C_5H_5)Fe(CO)(PPh_2(O-(*l*)-menthyl)nicotinoyl], shows a *cisoid* geometry [9]. Molecular modelling [2] of the conformational preferences of complex **1** in solution indicates that the *cisoid* and *transoid* conformations are energetically degenerate (Fig. 3). The ^{1}H NMR spectrum at room temperature of the benzoyl analogue, [(η^5-C_5H_5)Fe(CO)-(PPh_3)CO-3-phenyl], shows that the *ortho* protons are equivalent [18] thereby indicating rapid rotation about the CO–phenyl bond and, by analogy, rotation about the CO–pyridyl bond of **1** could reasonably be expected. Consistent with this hypothesis are n.O.e. experiments which have shown that in solution irradiation of the signal (δ 4.59), corresponding to the cyclopentadienyl ligand of **1**, enhances both the signal (δ 8.20) for the proton at the 2-position and the signal (δ 7.23) for the proton at the 4-position by 8% in each case. On the basis of the experimental evidence both conformers are expected to exist in solution. However, further modelling studies show that the 4-position of the *transoid* rotamer is more distant from the coordinated alkyllithium than the same centre in the *cisoid* arrangement. Consequently the reaction is expected to occur via the *cisoid* conformer (Fig. 3).

It is envisioned that initial coordination of the alkyl or aryllithium to the acyl oxygen of **1** occurs. This is likely to be extremely favourable given the high polarity of the acyl carbonyl group, as evidenced by its IR absorption at ν_{max} 1580 cm^{-1}. Directed alkylation then occurs toward the nicotinoyl 4-position. The n.O.e. experiments confirm the regioselectivity of reaction: when the N–CH_3 signal in the ^{1}H NMR spectrum of **5a** is irradiated two olefinic protons at δ 7.18 and 5.77 (C-2 and C-6, respectively) each show a 12% enhancement. Similarly, irradiation of the analogous signal of **5b** shows a 9% enhancement at both δ 7.45 and 5.86 for the olefinic C-2 and C-6 protons, respectively, thereby illustrating that in these reactions the nucleophile is being delivered to the 4-position. The predicted stereochemical course of the addition of alkyl and aryllithiums to **1** involves preferential approach of the nucleophile to the unhindered face of the nicotinoyl ring. As such, nucleophilic addition to the *cisoid* conformer would give rise to the (Fe-*RS*,4-*RS*) relative configuration of the iron to the 4-position in intermediates **2a** and **2c** (Fe-*RS*,4-*SR* for **2b**). This argument is analogous to that used to explain the remarkable stereoselectivities observed for Michael additions to α,β-unsaturated iron acyl complexes [19,20].

The X-ray crystal structure of complex **4a** confirms the predicted (Fe-*RS*,4-*RS*) relative stereochemistry, showing the proton at the 4-position oriented towards the triphenylphosphine. Molecular modelling shows that the preferred conformation of **4a** has the C-4 centre *cisoid* to the acyl carbonyl; the *transoid* orientation would introduce steric

[2] All conformational analyses discussed in this text were performed with CHEM-X [17].

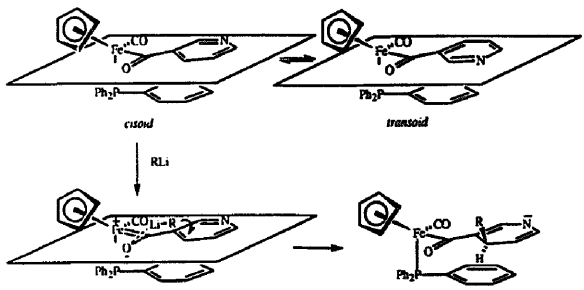


Fig. 3. Attack of the nucleophile to complex **1** in the *cisoid* conformation.

interactions between the alkyl substituent at C-4 and the bulky triphenylphosphine ligand. Consistent with these studies, the X-ray crystal structure of **4a** shows the C-4 centre is *cisoid* with respect to the acyl oxygen, which in turn is *anti* to the CO ligand [8]. As compounds **3** and **5** can be prepared from **4**, determination of the relative stereochemistry of **4a** allows the configuration of all these complexes to be confirmed as that illustrated in Scheme 1.

In conclusion, the stereoselective synthesis of 4-substituted-1,4-dihydronicotinoyl complexes has been achieved using the iron auxiliary $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)]$ to control the stereochemical course of the reaction. Efforts are currently being directed towards the preparation of these iron acyl complexes in homochiral form [21], their efficient decomplexation to carboxylic acids, esters and amides [8,22], and their potential application as effective NADH mimics.

4. Experimental

All reactions and purifications were performed under a nitrogen atmosphere using standard vacuum line and Schlenk tube techniques [23]. Removal of all solvents was carried out under reduced pressure. Tetrahydrofuran (THF) was dried over sodium benzophenone ketyl and distilled. Dichloromethane was distilled from calcium hydride and hexane refers to that fraction boiling in the range 67–70°C. Methyllithium (1.4 M in diethyl ether; low halide content) and n-butyllithium (1.6 M in hexane) was used as supplied by Aldrich. Phenyllithium (0.35 M in diethyl ether) was prepared from lithium wire and bromobenzene according to a literature method [24]. IR spectra were recorded in dichloromethane on a Perkin-Elmer 297 instrument. Proton NMR spectra were recorded on a Bruker WH 300 spectrophotometer at 300.13 MHz and referenced to residual protiosolvent, with chemical shifts being reported as δ ppm from $(CH_3)_4Si$. ^{13}C NMR spectra were recorded on a Bruker AM 250 spectrometer at 62.90 MHz using $CDCl_3$ as solvent and internal standard and are reported as δ ppm from $(CH_3)_4Si$. ^{31}P NMR spectra were recorded on a Bruker AM 250 spectrometer at 101.26 MHz using $CDCl_3$ as solvent and are reported as δ ppm from an external reference of triethylphosphate in D_2O. Mass spectra were recorded on a V.G. micromass ZAB 2F instrument using EI and FD techniques. Elemental analyses were performed by the University of Manchester Analytical Service and the Dyson Perrins Laboratory Analytical Service (Oxford, UK).

4.1. Preparation of $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)CO\text{-}3\text{-}pyridyl]$ (1)

Freshly distilled nicotinyl chloride (21.27 g, 150.2 mmol), prepared according to literature methods [11], was added over 20 min as a solution in THF (50 ml) to a stirred solution of $[(\eta^5\text{-}C_5H_5)Fe(CO)_2]^-Na^+$ (prepared from cyclopentadienyldicarbonyliron dimer (24.00 g, 67.8 mmol) in THF (400 ml) at −78°C. The mixture was stirred for 2 h at −78°C and then allowed to warm to ambient and stirred overnight. The solvent was removed, dichloromethane (500 ml) added and the resulting solution filtered through Celite. The crude product was concentrated and chromatographed over alumina (Grade I); purple–red cyclopentadienyldicarbonyliron dimer eluted first (1:1 hexane diethyl ether) followed by a yellow band (ethyl acetate). Removal of solvent from this fraction gave a yellow crystalline solid identified as $[(\eta^5\text{-}C_5H_5)Fe(CO)_2CO\text{-}3\text{-}pyridyl]$ (27.5 g, 72%). This intermediate (2.66 g, 9.4 mmol) was dissolved in a solution of triphenylphosphine (3.70 g, 14.1 mmol) in cyclohexane (140 ml) and was irradiated internally in a quartz immersion apparatus using a Hanovia 125 W medium pressure mercury arc lamp. The reaction was monitored by IR spectroscopy (disappearance of carbonyl stretches at 2100 and 1965 cm^{-1}) and irradiation stopped after 72 h. The product, an orange precipitate which coated the walls of the reaction vessel, was separated by filtration, washed with cyclohexane, then dissolved in CH_2Cl_2 and filtered through deactivated alumina (Grade V). The solvent was removed and the residue crystallised from hexane/CH_2Cl_2 to give **1** (3.94 g, 81%) as an orange crystalline solid. *Anal.* Found: C, 69.4; H, 4.8; N, 2.7; P, 5.8. Calc. for $C_{30}H_{24}FeNO_2P$: C, 69.65; H, 4.7; N 2.7; P, 6.0%. ν_{max} (cm^{-1}): 1940 vs (C≡O), 1580s (C=O). ^1H NMR ($CDCl_3$): δ 8.46 (1H, dd, $^3J_{HH}$ 4.7 Hz, $^4J_{HH}$ 1.6 Hz, 6-H), 8.20 (1H, d, $^4J_{HH}$ 1.5 Hz, 2-H), 7.50–7.28 (15H, m, Ph), 7.23 (1H, dt, $^3J_{HH}$ 7.9 Hz, $^4J_{HH}$ 1.9 Hz, 4-H), 7.12 (1H, dd, $^3J_{HH}$ 7.9, 4.8 Hz, 5-H), 4.59 (5H, d, $^3J_{PH}$ 1.3 Hz, C_5H_5).

$^{13}C\{^1H\}$ NMR: δ 220.43 (d, $^2J_{PC}$ 31.6 Hz, C=O), 149.46 (s, 6-C), 147.30 (s, 2-C), 146.61 (s, 3-C), 135.85 (d, $^1J_{PC}$ 43.6 Hz, Ph C_{ipso}), 133.31 (d, $^2J_{PC}$ 9.8 Hz, Ph C_{ortho}), 132.64 (s, 4-C), 129.87 (s, Ph, C_{para}), 128.13 (d, $^3J_{PC}$ 9.4 Hz, Ph C_{meta}), 122.43 (s, 5-C), 85.39 (s, C_5H_5). $^{31}P\{^1H\}$ NMR: δ 70.66. *m/z* 517 (M^+).

4.2. X-ray crystal structure analysis of (RS)-[(η⁵-C₅H₅)Fe(CO)(PPh₃)CO-3-pyridine (1)

$C_{30}H_{24}FeNO_2P$, monoclinic, space group $P2_1/n$, a = 16.359(2), b = 18.498(5), c = 8.031(1) Å, β = 94.88(1)°, U = 2421 Å^3, Z = 4, R = 0.029, R_w = 0.035.

4.3. General procedure for the sequential reaction of 1 with nucleophiles and electrophiles

Aklyl or aryllithium (0.9 mmol; 5.8 mmol in the case of methyllithium) was added to complex **1** (300 mg, 0.58 mmol) in THF (50 ml) at −78°C to give a deep red solution. The mixture was stirred at −78°C for 1 h (where methyllithium was the nucleophile the mixture was warmed to −40°C and stirred for a further 2 h then recooled to −78°C). Methanol (1 ml), chloroformate (3.2 mmol; 6.4 mmol when methyllithium was used), or dimethyl sulfate (0.25 ml, 2.64 mmol; 0.75 ml, 7.92 mmol when methyllithium was used) was added dropwise to give an orange solution. For complexes **3** and **4** the mixture was stirred at −78°C for a further 0.5 h, warmed to room temperature and the solvent removed. For complexes **5** the mixture was allowed to warm to ambient over 2 h, stirred for 1 h, saturated $NaHCO_3$ (20 ml) added, the resulting mixture stirred for 2 h, the organic layer separated, the aqueous layer washed with dichloromethane (2×30 ml) and the combined organic extracts were concentrated. The orange oil which was obtained from each reaction was extracted with dichloromethane (3×10 ml) and filtered through alumina (Grade V). The crude product complexes were analysed by ^1H NMR (300 MHz) spectroscopy to check diastereoselectivities. The product complexes were purified by chromatography on alumina (Grade V, **3a–c** eluted with 1:1 dichloromethane diethyl ether, **4a–c** and **5a,b** eluted with diethyl ether, any unreacted complex **1** eluted with dichloromethane), and crystallised from dichloromethane/hexane.

4.4. (Fe-RS,4-RS)-[(η⁵-C₅H₅)Fe(CO)(PPh₃)CO-3-(4-methyl-1,4-dihydropyridine)] (3a)

Red crystalline solid (80%). Found: *m/z* 533.1216 (M^+); calc. for $C_{31}H_{28}FeNO_2P$: 533.1207. ν_{max} (cm^{-1}): 3450s (N–H), 1900vs (C=O), 1665m (C=C), 1610s (C=O). ^1H NMR ($CDCl_3$): δ 7.63–7.28 (15H, m, Ph), 7.38 (1H, d, $^3J_{HH}$ 5.7 Hz, 2-H), 6.01 (1H, ddd, $^3J_{HH}$ 7.5, 4.4 Hz, $^4J_{HH}$ 0.7 Hz, 6-H), 5.39 (1H, bt, NH), 4.70 (1H, ddd, $^3J_{HH}$ 7.5, 6.5 Hz, $^4J_{HH}$ 1.7 Hz, 5-H), 4.41 (5H, d, $^3J_{PH}$ 1.1 Hz, C_5H_5), 2.75 (1H, dq, $^3J_{HH}$ 6.5, 6.5 Hz, 4-H), 0.86 (3H, d, $^3J_{HH}$ 6.5 Hz, CH_3). $^{13}C\{^1H\}$ NMR: δ 222.65 (d, $^2J_{PC}$ 36.5 Hz, C=O), 142.98 (s, 2-C), 137.04 (d, $^1J_{PC}$ 42.0 Hz, Ph C_{ipso}), 133.45 (d, $^2J_{PC}$ 9.5 Hz, Ph C_{ortho}), 130.34 (d, $^3J_{PC}$ 3.5 Hz, 3-C)′ [3], 129.39 (s, Ph C_{para}), 127.88 (d, $^3J_{PC}$ 9.4 Hz, Ph C_{meta}), 123.41 (s, 6-C), 109.44 (s, 5-C), 85.44 (s, C_5H_5), 27.98 (s, 4-C), 24.57 (s, CH_3). $^{31}P\{^1H\}$ NMR: δ 73.68.

4.5. (Fe-RS,4-SR)-[(η⁵-C₅H₅)Fe(CO)(PPh₃)CO-3-(4-phenyl-1,4-dihydropyridine)] (3b)

Orange crystalline solid (81%). Found: *m/z* 595.1338 (M^+); calc. for $C_{36}H_{30}FeNO_2P$: 595.1343. ν_{max} (cm^{-1}): 3450s (N–H), 1905vs (C=O), 1665m (C=C), 1610s (C=O). ^1H NMR ($CDCl_3$): δ 7.61 (1H, d, $^3J_{HH}$ 5.6 Hz, 2-H), 7.50–6.95 (20H, m, Ph), 6.08 (1H, dd, $^3J_{HH}$ 7.4, 4.3 Hz, 6-H), 5.51 (1H, bt, NH), 4.81 (1H, ddd, $^3J_{HH}$ 7.4, 5.4 Hz, $^4J_{HH}$ 1.6 Hz, 5-H), 4.25 (5H, d, $^3J_{PH}$ 1.1 Hz, C_5H_5), 3.98 (1H, d, $^3J_{HH}$ 5.4 Hz, 4-H). $^{13}C\{^1H\}$ NMR (CD_2Cl_2)″ [4]: δ 223.19 (d, $^2J_{PC}$ 35.8 Hz, C=O), 149.96 (s, Ph C_{ipso}), 143.64 (s, 2-C), 137.50 (d, $^1J_{PC}$ 42.4 Hz, PPh_3 C_{ipso}), 133.89 (d, $^2J_{PC}$ 9.6 Hz, PPh_3 C_{ortho}), 129.1 (s, PPh_3 C_{para}), 128.61 (s, Ph C_{ortho}), 128.31 (d, $^3J_{PC}$ 9.6 Hz, PPh_3 C_{meta}), 127.17 (s, Ph C_{meta}), 125.64 (s, Ph C_{para}), 123.36 (s, 6-C), 108.64 (s, 5-C), 85.82 (s, C_5H_5), 40.06 (s, 4-C). $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ 73.85.

4.6. (Fe-RS,4-RS)-[(η⁵-C₅H₅)Fe(CO)(PPh₃)CO-3-(4-n-butyl-1,4-dihydropyridine)] (3c)

Red crystalline solid (73%). Found: *m/z* 575.1685 (M^+); calc. for $C_{34}H_{34}FeNO_2P$: 575.1676. ν_{max} (cm^{-1}): 3450s (N–H), 1900vs (C=O), 1665m (C=C), 1610s (C=O). ^1H NMR ($CDCl_3$): δ 7.55–7.27 (15H, m, Ph), 7.44 (1H, d, $^3J_{HH}$ 5.6 Hz, 2-H), 6.08 (1H, ddd, $^3J_{HH}$ 7.6, 4.3 Hz, $^4J_{HH}$ 0.7 Hz, 6-H), 5.37 (1H, bt, NH), 4.68 (1H, ddd, $^3J_{HH}$ 7.5, 5.5 Hz, $^4J_{HH}$ 1.7 Hz, 5-H), 4.41 (5H, d, $^3J_{PH}$ 1.2 Hz, C_5H_5), 2.78 (1H, m, 4-H), 1.30–1.08 (6H, m, $(CH_2)_3CH_3$), 0.84 (3H, t, $^3J_{HH}$ 6.6 Hz, CH_3). $^{13}C\{^1H\}$ NMR: δ 222.76 (d, $^2J_{PC}$ 35.1 Hz, C=O), 143.61 (s, 2-C), 137.13 (d, $^1J_{PC}$ 42.2 Hz, Ph C_{ipso}), 133.50 (d, $^2J_{PC}$ 9.3 Hz, Ph C_{ortho}), 129.35 (s, Ph C_{para}), 128.86 (d, $^3J_{PC}$ 5.0 Hz, 3-C)′, 127.86 (d, $^3J_{PC}$ 9.3 Hz, Ph C_{meta}), 124.17 (s, 6-C), 107.61 (s, 5-C), 85.41 (s, C_5H_5), 37.51 (s, CH_2), 33.10 (s, 4-C), 26.98 (s, CH_2), 23.13 (s, CH_2), 14.25 (s, CH_3). $^{31}P\{^1H\}$ NMR: δ 73.60.

4.7. (Fe-RS,4-RS)-[(η⁵-C₅H₅)Fe(CO)(PPh₃)CO-3-(N-methoxycarbonyl-4-methyl-1,4-dihydropyridine)] (4a)

Orange crystalline solid (66%). *Anal.* Found: C, 66.8; H, 5.2; N, 2.3. Calc. for $C_{33}H_{30}FeNO_4P$: C, 67.0; H, 5.1; N, 2.4%. ν_{max} (cm^{-1}): 1910vs (C=O), 1720s (C=O), 1675m (C=C), 1560s (C=O). ^1H NMR (DMSO-d^6, 333 K): δ 7.96 (1H, d, $^4J_{HH}$ 1.3 Hz, 2-H), 7.45–7.35 (15H, m, Ph),

[3] Superscript prime (′): weak resonance.

[4] Superscript double prime (″): dihydropyridine C-3 resonance not detected.

6.71 (1H, dd, $^3J_{HH}$ 7.9 Hz, $^4J_{HH}$ 1.3 Hz, 6-H), 5.05 (1H, dd, $^3J_{HH}$ 7.9, 5.1 Hz, 5-H), 4.44 (5H, d, $^3J_{PH}$ 1.1 Hz, C_5H_5), 3.87 (3H, s, OCH_3), 2.50 (1H, dq, $^3J_{HH}$ 6.7, 5.1 Hz, 4-H), 0.84 (3H, d, $^3J_{HH}$ 6.6 Hz, CH_3). $^{13}C\{^1H\}$ NMR: δ 221.34 (d, $^2J_{PC}$ 35.1 Hz, C=O), 152.19 (s, CO_2Me), 137.63 (bs, 2-C), 136.76 (d, $^1J_{PC}$ 43.0 Hz, Ph C_{ipso}), 133.42 (d, $^2J_{PC}$ 9.4 Hz, Ph C_{ortho}), 129.56 (s, Ph C_{para}), 128.01 (d and s, $^3J_{PC}$ 9.2 Hz, Ph C_{meta} and 3-C), 120.99 (s, 6-C), 115.76 (s, 5-C), 85.35 (s, C_5H_5), 53.71 (s, OCH_3), 28.10 (s, 4-C), 24.13 (s, CH_3). $^{31}P\{^1H\}$ NMR: δ 73.35.

4.8. X-ray crystal structure analysis of 4a

$C_{33}H_{30}NO_4PFe$, monoclinic, space group $P2_1/n$, a = 11.683(3), b = 18.290(7), c = 13.845(5) Å, β = 98.72(3)°, U = 2924(2) Å^3, Z = 4, R = 0.089, R_w = 0.078.

4.9. (Fe-RS,4-SR)-[(η^5-C_5H_5)Fe(CO)(PPh_3)CO-3-(N-methoxycarbonyl-4-phenyl-1,4-dihydropyridine)] (4b)

Orange crystalline solid (90%). *Anal.* Found: C, 69.9; H, 5.2; N, 2.3. Calc. for $C_{38}H_{32}FeNO_4P$: C, 69.8; H, 4.9; N, 2.1%. ν_{max} (cm^{-1}): 1915vs (C=O), 1725s (C=O), 1675m (C=C), 1560s (C=O). ^1H NMR (DMSO-d^6, 333 K): δ 8.22 (1H, d, $^4J_{HH}$ 1.3 Hz, 2-H), 7.76–6.97 (20H, m, Ph), 6.79 (1H, dd, $^3J_{HH}$ 7.9 Hz, $^4J_{HH}$ 1.1 Hz, 6-H), 5.12 (1H, dd, $^3J_{HH}$ 7.9, 5.2 Hz, 5-H), 4.26 (5H, d, $^3J_{PH}$ 1.2 Hz, C_5H_5), 3.91 (3H, s, OCH_3), 3.74 (1H, $^3J_{HH}$ 5.2, 4-H). $^{13}C\{^1H\}$ NMR: δ 220.01 (d, $^2J_{PC}$ 39.1 Hz, C=O), 152.19 (s, CO_2Me), 145.90 (s, Ph C_{ipso}), 136.67 (d, $^1J_{PC}$ 41.5 Hz, PPh_3 C_{ortho}), 134.80 (bs, 2-C), 133.44 (d, $^2J_{PC}$ 9.8 Hz, PPh_3 C_{ortho}), 130.02 (s, 3-C)′, 129.53 (s, PPh_3 C_{para}), 128.21 (Ph C_{ortho}), 127.95 (d, $^3J_{PC}$ 7.3 Hz, PPh_3 C_{meta}), 127.87 (s, Ph C), 127.61 (s, Ph C), 125.95 (s, Ph C), 120.75 (s, 6-C), 113.80 (s, 5-C), 85.31 (s, C_5H_5), 53.79 (s, OCH_3), 39.25 (s, 4-C). $^{31}P\{^1H\}$ NMR: δ 72.95. m/z 653 (M^+).

4.10. (Fe-RS,4-RS)-[(η^5-C_5H_5)Fe(CO)(PPh_3)CO-3-(N-methoxycarbonyl-4-n-butyl-1,4-dihydropyridine)] (4c)

Red crystalline solid (78%). *Anal.* Found: C, 68.3; H, 5.9; N, 2.2. Calc. for $C_{36}H_{36}FeNO_4P$: C, 68.25; H, 5.7; N, 2.2%. ν_{max} (cm^{-1}): 1910vs (C=O), 1720s (C=O), 1675m (C=C), 1615s (C=O). ^1H NMR (DMSO-d^6, 333 K)″: δ 7.99 (1H, d, $^4J_{HH}$ 1.4 Hz, 2-H), 7.47–7.32 (15H, m, Ph), 6.77 (1H, dd, $^3J_{HH}$ 8.0 Hz, $^4J_{HH}$ 1.3 Hz, 6-H), 5.05 (1H, dd, $^3J_{HH}$ 8.0, 5.1 Hz, 5-H), 4.43 (5H, d, $^3J_{PH}$ 1.1 Hz, C_5H_5), 3.87 (3H, s, OCH_3), 2.53 (1H, m, 4-H), 1.32–1.04 (6H, m, $(CH_2)_3CH_3$), 0.80 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_3). $^{13}C\{^1H\}$ NMR: δ 221.87 (d, $^2J_{PC}$ 35.1 Hz, C=O), 152.28 (s, CO_2Me), 138.17 (bs, 2-C), 136.80 (d, $^1J_{PC}$ 42.6 Hz, Ph C_{ipso}), 133.45 (d, $^2J_{PC}$ 9.4 Hz, Ph C_{ortho}), 129.54 (s, Ph C_{para}), 127.98 (d, $^3J_{PC}$ 9.3 Hz, Ph C_{meta}), 121.87 (s, 6-C), 114.05 (s, 5-C), 85.30 (s, C_5H_5), 53.61 (s, OCH_3), 36.62 (s, CH_2), 33.07 (s, 4-C), 27.16 (s, CH_2), 22.86 (s, CH_2), 14.10 (s, CH_3). $^{31}P\{^1H\}$ NMR: δ 73.36. m/z 633 (M^+), 605 ($M^+ - 28$).

4.11. (Fe-RS,4-RS)-[(η^5-C_5H_5)Fe(CO)(PPh_3)CO-3-(N-phenoxycarbonyl-4-methyl-1,4-dihydropyridine)] (4d)

Orange crystalline solid (63%). *Anal.* Found: C, 70.0; H, 4.9; N, 2.0. Calc. for $C_{38}H_{32}FeNO_4P$: C, 69.8; H, 4.9; N, 2.1%. ν_{max} (cm^{-1}): 1910vs (C=O), 1725s (C=O), 1675m (C=C), 1620s (C=O). ^1H NMR (DMSO-d^6, 365 K): δ 8.10 (1H, s, 2-H), 7.50–7.30 (20H, m, Ph), 6.86 (1H, d, $^3J_{HH}$ 8.0 Hz, 6-H), 5.17 (1H, dd, $^3J_{HH}$ 8.0, 5.0 Hz, 5-H), 4.45 (5H, d, $^3J_{PH}$ 1.0 Hz, C_5H_5), 2.61 (1H, m, $^3J_{HH}$ 6.6, 5.0 Hz, 4-H), 0.93 (3H, d, $^3J_{HH}$ 6.6 Hz, CH_3). $^{13}C\{^1H\}$ NMR″: δ 221.70 (d, C=O)′, 150.97 (s, CO_2Ph), 150.14 (s, Ph C_{ipso}), 137.38 (s, 2-C), 136.76 (d, $^1J_{PC}$ 42.6 Hz, PPh_3 C_{ipso}), 133.43 (d, $^2J_{PC}$ 9.5 Hz, PPh_3 C_{ortho}), 129.59 (s), 129.46 (s) (PPh_3 C_{para} and Ph C_{ortho}), 128.02 (d, $^2J_{PC}$ 9.5 Hz, PPh_3 C_{meta}), 125.95 (s, Ph C_{para}), 121.55 (s, Ph C_{meta}), 120.91 (s, 6-C), 116.64 (s, 5-C), 85.34 (s, C_5H_5), 28.18 (s, 4-C), 24.09 (s, CH_3). $^{31}P\{^1H\}$ NMR: δ 73.30 (bd). m/z 653 (M^+), 625 ($M^+ - 28$).

4.12. (Fe-RS,4-RS)-[(η^5-C_5H_5)Fe(CO)(PPh_3)CO-3-(N-methyl-4-methyl-1,4-dihydropyridine)] (5a)

Orange crystalline solid (66%). Found: m/z 547.1358 (M^+); calc. for $C_{32}H_{30}FeNO_2P$: 547.1363. ν_{max} (cm^{-1}): 1905vs (C=O), 1660m (C=C), 1585s (C=O). ^1H NMR ($CDCl_3$): δ 7.57–7.28 (15H, m, Ph), 7.18 (1H, d, $^4J_{HH}$ 1.3 Hz, 2-H), 5.77 (1H, dd, $^3J_{HH}$ 7.4 Hz, $^4J_{HH}$ 1.5 Hz, 6-H), 4.71 (1H, dd, $^3J_{HH}$ 7.5, 5.4 Hz, 5-H), 4.42 (5H, d, $^3J_{PH}$ 1.0 Hz, C_5H_5), 3.15 (3H, s, NCH_3), 2.71 (1H, dq, $^3J_{HH}$ 6.4, 6.0 Hz, 4-H), 0.81 (3H, d, $^3J_{HH}$ 6.5 Hz, CH_3). $^{13}C\{^1H\}$ NMR: δ 222.77 (d, $^2J_{PC}$ 36.9 Hz, C=O), 147.91 (s, 2-C), 137.06 (d, $^1J_{PC}$ 42.2 Hz, Ph C_{ipso}), 133.43 (d, $^2J_{PC}$ 9.7 Hz, Ph C_{ortho}), 129.70 (d, $^3J_{PC}$ 3.5 Hz, 3-C), 129.33 (s, Ph C_{para}), 128.23 (s, 6-C), 127.83 (d, $^3J_{PC}$ 9.3 Hz, Ph C_{meta}), 110.26 (s, 5-C), 85.43 (s, C_5H_5), 41.30 (s, NCH_3), 27.72 (s, 4-C), 25.07 (s, CH_3). $^{31}P\{^1H\}$ NMR: δ 73.66.

4.13. (Fe-RS,4-SR)-[(η^5-C_5H_5)Fe(CO)(PPh_3)CO-3-(N-methyl-4-phenyl-1,4-dihydropyridine)] (5b)

Orange crystalline solid (75%). Found: m/z 609.1527 (M^+); calc. for $C_{37}H_{32}FeNO_2P$: 609.1526. ν_{max} (cm^{-1}): 1900vs (C=O), 1660m (C=C), 1590s (C=O). ^1H NMR ($CDCl_3$): δ 7.53–7.06 (21H, m. Ph and 2-H), 5.86 (1H, dd, $^3J_{HH}$, 7.4 Hz, $^4J_{HH}$ 1.4 Hz, 6-H), 4.83 (1H, dd, $^3J_{HH}$ 7.4, 5.5 Hz, 5-H), 4.28 (5H, d, $^3J_{PH}$ 1.1 Hz, C_5H_5), 3.95 (1H, d, $^3J_{HH}$ 5.5 Hz, 4-H), 3.20 (3H, s, CH_3). $^{13}C\{^1H\}$ NMR: δ 222.98 (d, $^2J_{PC}$ 35.5 Hz, C=O), 148.77 (s, Ph C_{ipso}), 146.73 (s, 2-C), 137.04 (d, $^1J_{PC}$ 41.7 Hz, PPh_3 C_{ipso}), 133.49 (d, $^2J_{PC}$ 9.5 Hz, PPh_3 C_{ortho}), 129.35 (s, PPh_3 C_{para}), 128.08 (s, Ph C_{ortho}), 127.84 (d, $^3J_{PC}$ 9.2 Hz, PPh_3 C_{meta}), 127.04 (s), 126.91 (s), 125.82 (s), 125.82 (s), 125.28 (s) (Ph C_{meta}, Ph C_{para}, 3-C and 6-C), 108.61 (s, 5-C), 85.43 (s, C_5H_5), 41.40 (s, 4-C), 38.73 (s, CH_3). $^{31}P\{^1H\}$ NMR: δ 73.32.

4.14. Preparation of (Fe-RS,4-SR)-[(η^5-C_5H_5)Fe(CO)-(PPh_3)CO-3-(4-phenyl-1,4-dihydropyridine)] (3b) from (Fe-RS,4-SR)-[(η^5-C_5H_5)Fe(CO)(PPh_3)CO-3-(N-methoxycarbonyl-4-phenyl-1,4-dihydropyridine)] (4b)

Methyllithium (0.5 ml, 0.8 mmol) was added to complex **4b** (118 mg, 0.18 mmol) in THF (20 ml) at −78°C. The mixture was stirred for 1 h at −40°C and for a further hour at −25°C to give a dark red solution. The mixture was cooled to −60°C methanol (2 ml) added, slowly warmed to ambient and the solvent removed. The orange residue was extracted with dichloromethane (3×10 ml) and filtered through alumina (Grade V), the solvent removed and the residue dried under vacuum to give pure complex **3b** as an orange amorphous solid (106 mg, 98%), identical to the sample prepared previously.

4.15. Preparation of (Fe-RS,4-SR)-[(η^5-C_5H_5)Fe(CO)-(PPh_3)CO-3-(N-methyl-4-phenyl-1,4-dihydropyridine)] (5b) from (Fe-RS,4-SR)-[(η^5-C_5H_5)Fe(CO)(PPh_3)CO-3-(N-methoxycarbonyl-4-phenyl-1,4-dihydropyridine)] (4b)

Methyllithium (1.3 ml, 1.82 mmol) was added to an orange solution of complex **4b** (296 mg, 0.45 mmol) in THF (40 ml) at −78°C. The mixture was warmed to −30°C and stirred for 1 h to give a dark red solution. The mixture was cooled to −78°C, dimethyl sulfate (0.25 ml, 2.64 mmol) added, stirred at −40°C for 1 h, warmed to ambient and stirred for a further hour to give a light red solution. Saturated $NaHCO_3$ aq. (2 ml) was added, the resulting mixture stirred for 2 h and the solvent removed. Dichloromethane (30 ml) and water (30 ml) were added, the organic phase separated, the solvent removed and the residue dried. Filtration of a dichloromethane solution of the crude product through alumina (Grade V) gave pure complex **5b** as an orange amorphous solid (261 mg, 94%). Crystallisation from a dichloromethane/hexane solution afforded **5b** which was identical to the sample prepared above.

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