S0957-4166(96)00159-0

Synthesis of Phosphinoferrocenyloxazolines. New Ligands for Asymmetric Catalysis

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Abstract: Condensation of β-hydroxy alcohols with ferrocenyl chloride gave the corresponding amides which were dehydrated to give ferrocenyl oxazolines in good overall yield. Subsequent lithiation with *n*-BuLi in the presence of TMEDA and addition of PPh_2Cl led to the isolation of (S)-(S)-^iPr-phosferrox and (S)-(S)-Me-phosferrox ligands **1** and **2**. Their corresponding diastereoisomers, (S)-(R)-^iPr-phosferrox and (S)-(R)-Me-phosferrox **3** and **4** were obtained *via* the intermediacy of removable trimethylsilyl blocking groups. The CD spectra of **1** - **4** and their parent ferrocenyl oxazolines **9** and **10** were obtained.
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Introduction

Ferrocene-derived ligands utilise the planar chirality that results when the ferrocene nucleus contains two different substituents attached to a cyclopentadienyl ring.[1] Of the examples known, most are derived from *N,N*-dimethyl-1-ferrocenylethylamine as this can be obtained enantiomerically pure by classical resolution[2] or asymmetric synthesis.[3] In contrast, oxazoline ligands exploit the tetrahedral stereocentres inherent in the amino acids from which they are derived. On coordination, their 4-substituent lies proximal to the metal thereby influencing the stereoselectivity of catalysed reactions.[4] In particular, phosphinoaryloxazolines containing electronically unsymmetrical nitrogen and phosphorous coordinating groups, have proved to be very successful ligands for asymmetric allylic substitution reactions.[5] Thus attaching oxazolines to an appropriate ferrocene nucleus has the potential benefits of cooperatively combining the tetrahedral chirality inherent in the oxazoline with the planar chirality of disubstituted ferrocenes.[6]
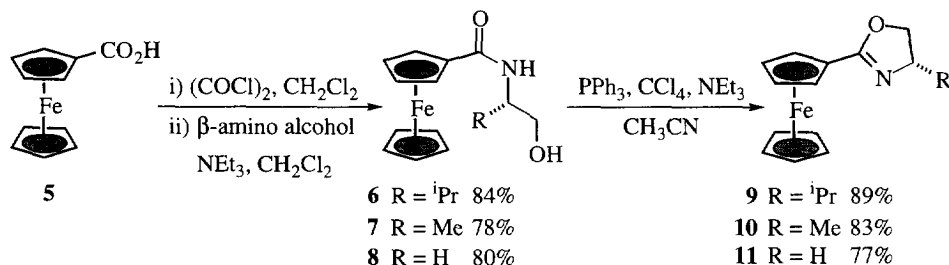

1	**2**	**3**	**4**
(S)-(S)-^iPr-phosferrox	(S)-(S)-Me-phosferrox	(S)-(R)-^iPr-phosferrox	(S)-(R)-Me-phosferrox
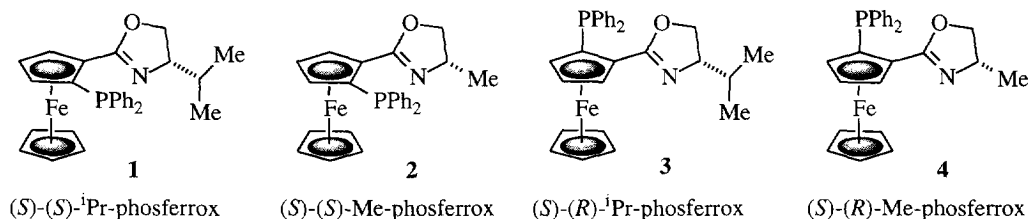
Phosferrox ligands

In this work we report on the synthesis of phosphinoferrocenyloxazoline (phosferrox) ligands **1 - 4**. All of these compounds are air-stable, yellow, crystalline solids, readily obtained in only a few steps from commercially available starting materials. Part of this work has appeared as a preliminary communication.[7]

Results and discussion

Prior to this work there had been only one report on the synthesis of 2-ferrocenyl oxazolines, obtained by condensation of aziridines with ferrocenyl chloride followed by acid catalysed rearrangement to generate the 5-membered ring.[8] For ease of synthesis we sought a method that directly utilised commercially available β-amino alcohols. Thus ferrocenyl chloride, generated *in situ* from ferrocenecarboxylic acid **5**[9] and oxalyl chloride, was combined with a range of β-amino alcohols resulting in isolation of the β-hydroxy amides **6 - 8** in good yield. These were subsequently cyclised and dehydrated under Appel conditions[10] with PPh₃, CCl₄ and NEt₃ yielding the 2-ferrocenyl oxazolines **9 - 11**, also in good yield (Scheme 1). Oxazoline **11** was found to have a m.p. and spectroscopic data essentially identical to that reported for the compound previously obtained by the aziridine methodology.[8]

5 → i) (COCl)₂, CH₂Cl₂ / ii) β-amino alcohol, NEt₃, CH₂Cl₂ →
6 R = ⁱPr 84%
7 R = Me 78%
8 R = H   80%

→ PPh₃, CCl₄, NEt₃, CH₃CN →
9 R = ⁱPr 89%
10 R = Me 83%
11 R = H   77%

Scheme 1

Lithiation of **9** was initially investigated using *n*-BuLi in Et₂O at room temperature followed by addition of PPh₂Cl to give a 2.5 : 1 ratio of diastereoisomers. The major isomer was isolated pure in 38% yield after recrystallisation of the mixture from hexane and shown by X-ray crystal structure analysis to be (*S*)-(*S*)-ⁱPr-phosferrox **1**.[7a] Subsequent to this initial investigation, a report appeared on highly diastereoselective lithiation/silylation sequences with **9** when TMEDA was a component of the reaction mixture.[11] Repetition of this lithiation methodology with *n*-BuLi and TMEDA in Et₂O, which had previously been shown to give a 100 : 1 diastereoselectivity, followed by addition of PPh₂Cl produced **1** essentially diastereomerically pure in 64% yield (Scheme 2). When applied to oxazoline **10** this lithiation methodology also proceeded with good selectivity (see later) such that **2** was isolated in 59% after recrystallisation to remove traces of the minor diastereoisomer.
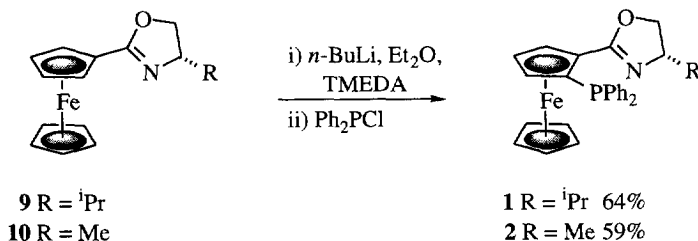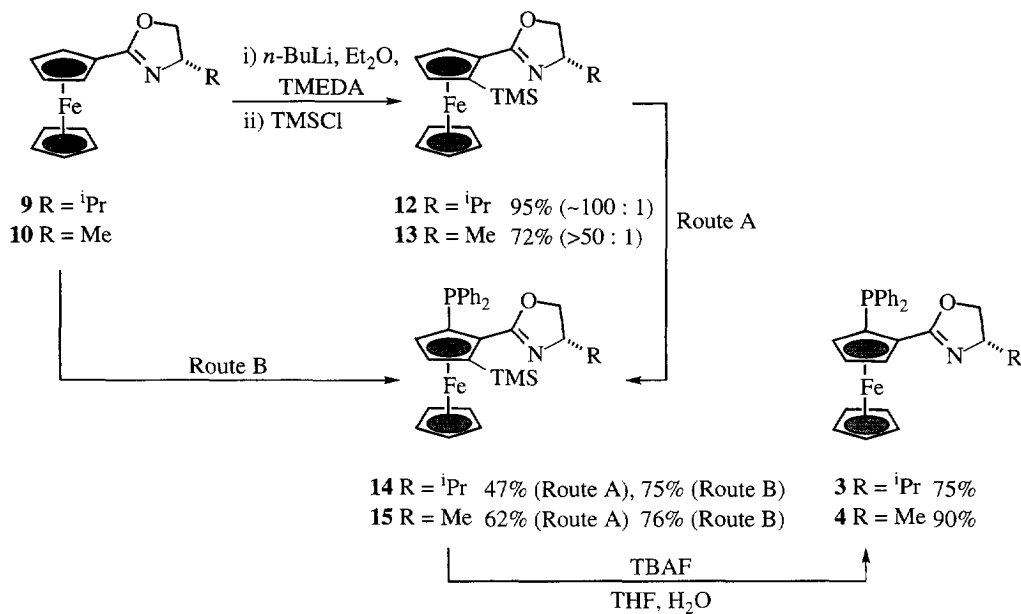
Scheme 2

The origin of the diastereoselection can be accounted for by the two rotamers **A** and **B** shown in Scheme 3. If the butyllithium aggregate coordinates to the oxazoline nitrogen and lies *exo* to the ferrocenyl group, there is an unfavourable interaction with the R group in **B** which is not present in **A**. In the absence of butyllithium, molecular modelling reveals that there is essentially no difference in the energies of **A** and **B** as the R groups (^{i}Pr, Me) lie remote from the unsubstituted cyclopentadienyl ring in **A**. Thus the position of metallation is determined by the lithiating aggregate avoiding repulsive interactions with both the ferrocenyl group and oxazoline R substituent.[12]
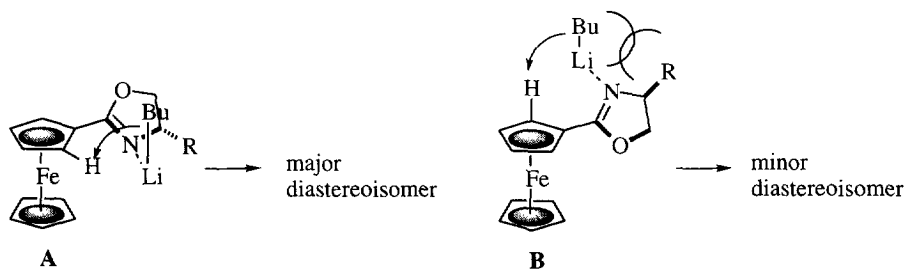
Scheme 3

The (*S*)-(*R*)-phosferrox ligands **3** and **4** were synthesised through the use of a removable trimethylsilyl blocking group.[13] Application of the TMEDA based lithiation followed by addition of TMSCl gave **12** in excellent yield and with a diastereoselectivity essentially identical to that previously reported (Scheme 4).[11] When applied to **10** this methodology gave a greater than 50 : 1 selectivity and the minor isomer was removed by column chromatography to give **13** in good yield. The remaining unsubstituted *ortho* ferrocenyl oxazoline positions in both **12** and **13** were lithiated on treatment with *n*-BuLi, addition of PPh$_2$Cl providing the trisubstituted derivatives **14** and **15**.[14] In light of the high selectivities found with the TMEDA based lithiations, it proved possible to obtain both **14** and **15** directly using one-pot procedures, where initial lithiation/silylation is followed directly by lithiation/phosphorylation (Route B, Scheme 4). In both cases, the yields of the trisubstituted products were significantly increased. Finally, the trimethylsilyl groups were easily removed on heating at reflux THF/H$_2$O solutions of **14** and **15** containing TBAF to give (*S*)-(*R*)-^{i}Pr-phosferrox **3** and (*S*)-(*R*)-Me-phosferrox **4** in overall yields of 56% and 68% respectively from their parent ferrocenyl oxazolines.

9 R = ^{i}Pr
10 R = Me

i) *n*-BuLi, Et$_2$O, TMEDA
ii) TMSCl

12 R = ^{i}Pr   95% (~100 : 1)
13 R = Me   72% (>50 : 1)

Route A

Route B

14 R = ^{i}Pr   47% (Route A), 75% (Route B)   **3** R = ^{i}Pr   75%
15 R = Me   62% (Route A)   76% (Route B)   **4** R = Me   90%

TBAF
THF, H$_2$O

Scheme 4

The CD spectra of ferrocenyl oxazolines **9** and **10** are shown in Figure 1. Interestingly, despite these two compounds certainly having the same absolute configuration, they display Cotton effects of opposite sign for the major signals found at approximately 460 nm. This suggests that the two compounds have dissimilar conformations (in CHCl$_3$) resulting in different expressions of the tetrahedral chirality at the metal. However, this does not have a significant bearing on the lithiation steps as diastereoisomers of the same configuration are formed from **9** and **10**.
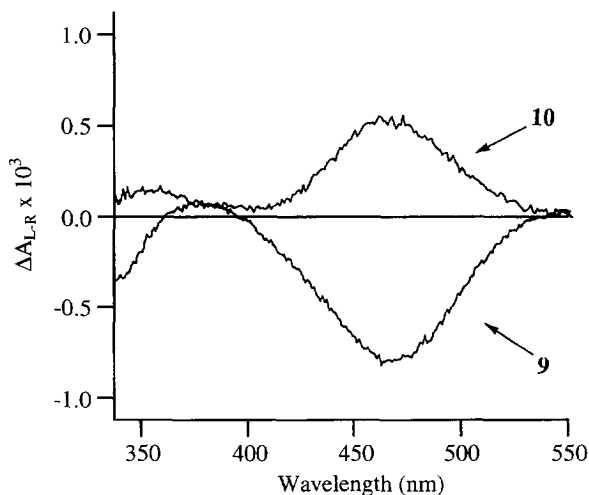

Figure 1. CD spectra of ferrocenyl oxazolines **9** and **10**

For (S)-(S)-Me-phosferrox **2** and (S)-(R)-Me-phosferrox **4** (Figure 2) their opposite elements of planar chirality are clearly apparent in the opposite signs for the two major bands at approximately 310 and 455 nm. Similarly for (S)-(S)-^{i}Pr-phosferrox **1** and (S)-(R)-^{i}Pr-phosferrox **3** (Figure 3), the bands around 310 nm are of the same sign as their corresponding methyl derivatives indicating that these bands may be used to assign the absolute configuration of planar chirality in -PPh$_2$ substituted ferrocenyl oxazolines. The large differences in the spectra of **1** and **3** in the region from 400 to 550 nm may again arise due to different conformational preferences of the two diastereoisomers containing the relatively bulky isopropyl substituent. However, changing the temperature of these solutions from room temperature to +50 °C and -40 °C made little difference to the appearance of the recorded spectra.
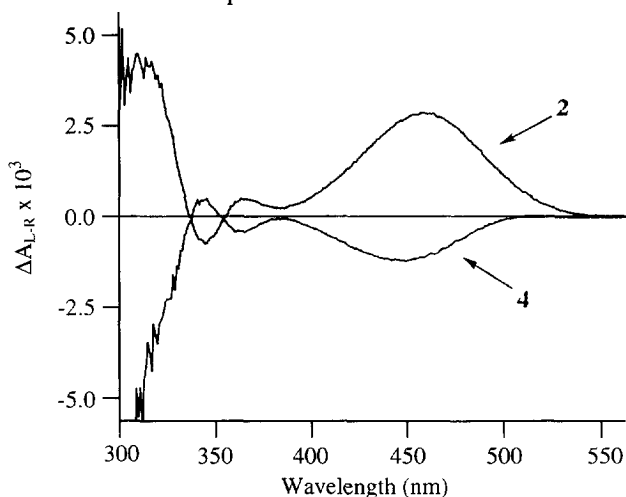

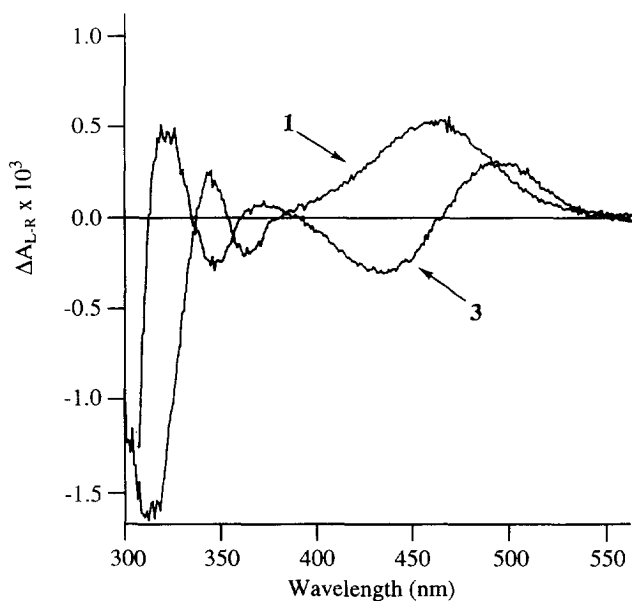**Figure 2**. CD spectra of (S)-(S)-Me-phosferrox **2** and (S)-(R)-Me-phosferrox **4**

Figure 3. CD spectra of (S)-(S)-^{i}Pr-phosferrox **1** and (S)-(R)-^{i}Pr-phosferrox **3**

In conclusion, we have reported on the synthesis of examples of a new class of ferrocene-derived ligands that have the potential to be systematically optimised for a given asymmetric reaction. We[15] and others[7d] have reported initial applications of such ligands and further investigation into their potential is in progress.

Experimental

Diethyl ether and tetrahydrofuran were distilled from sodium benzophenone ketyl and dichloromethane from calcium hydride. Petroleum ether refers to that fraction boiling in the range 40-60 °C and hexane to the fraction boiling in the range 65.5-70 °C. Chlorodiphenylphosphine was freshly distilled prior to use and TMEDA was distilled from calcium hydride. All other reagents were used as obtained commercially. Column chromatography was performed on SiO_2 (40-63 mm). Melting points were determined on a Gallenkamp digital melting point apparatus and a Kofler hot stage, and are not corrected. Rotations were recorded on a Optical Activity AA-1000 polarimeter (concentrations c given as g/100 ml) and CD spectra on a Jobin-Yvon DCV spectrometer. Elemental analyses were performed on a Perkin Elmer 240C Elemental Analyser. IR spectra were obtained on a Perkin-Elmer 1600 FTIR spectrometer. NMR spectra were recorded on a Bruker AMX 360 (360 MHz ^1H and 90 MHz ^{13}C) spectrometer. Mass spectra were recorded on a Fisons VG Platform II.

Synthesis of amides **6, 7** *and* **8**.

The following method for the synthesis of (2S)-N-(1-hydroxy-3-methylbutyl)ferrocenamide **6** is representative.

To a stirred suspension of ferrocenecarboxylic acid (1.033 g, 4.49 mmol) in CH_2Cl_2 (15 ml) at room temperature under nitrogen, was added *via* syringe oxalyl chloride (0.79 ml, 9 mmol). Gas evolution was accompanied by the formation of a dark red homogeneous solution after 10 min. The reaction mixture was stirred for an additional 10 min., followed by removal of the solvent *in vacuo*. The resultant crude ferrocenyl chloride, isolated as a dark oil that crystallised on standing, was taken up in CH_2Cl_2 (10 ml) and added *via* syringe to a solution of (S)-(+)-valinol (0.554 g, 5.37 mmol) and NEt_3 (1.25 ml, 9 mmol) in CH_2Cl_2 (7 ml) at room temperature under nitrogen. After stirring overnight, the dark reaction mixture was washed with H_2O (2 x 20 ml), dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (3% MeOH/CH_2Cl_2) to give the amide as a yellow crystalline solid (1.184 g, 84%).

m.p. 109-110 °C; $[\alpha]_D^{21}$ = -8 (c 1.34, EtOH) (Found: C, 61.11; H, 6.74; N, 4.21. $C_{16}H_{21}FeNO_2$ requires C, 60.97; H, 6.72; N, 4.44%); ν_{max} (nujol) 3284 (N-H), 3192 (O-H), 1611 (C=O amide I), 1551 (amide II) cm^{-1}; δ_H (CDCl$_3$) 0.97 (3 H, d, J 6.8, -CH$_3$), 0.98 (3 H, d, J 6.8, -CH$_3$), 1.93 (1 H, octet, J 6.8, -CH(CH$_3$)$_2$), 2.71 (1 H, brt, -OH), 3.65 - 3.83 (3 H, m, -CH$_2$OH and -NHCH-), 4.16 (5 H, s, C$_5$H$_5$), 4.30 (2 H, brs, Fc), 4.60 (1 H, brs, Fc), 4.62 (1 H, brs, Fc), 5.80 (1 H, brd, -NH-); δ_C {^1H} (CDCl$_3$) 19.04 (-CH$_3$), 19.69 (-CH$_3$), 28.99 (-CH(CH$_3$)$_2$), 57.01 (-NHCH-), 63.87 (-OCH$_2$-), 67.91 (Fc), 68.42 (Fc), 69.75 (C$_5$H$_5$), 70.46 (Fc), 70.51 (Fc), 75.95 (Fc - *ipso*), 171.37 (C=O); m/z (EI) 315 (M$^+$, 100%), 213 (81).

Similarly prepared were:

(2S)-N-(1-hydroxypropyl)ferrocenamide **7** isolated as a yellow crystalline solid by column chromatography (5% MeOH/CH_2Cl_2), yield = 78%.

m.p. 168.5-169.5 °C; $[\alpha]_D^{27}$ = +28 (c = 0.2, EtOH) (Found: C, 58.71; H, 6.20; N, 4.91. $C_{14}H_{17}FeNO_2$ requires C, 58.56; H, 5.97; N, 4.88%); ν_{max} (nujol) 3294 (N-H), 1628 (C=O amide 1), 1537 (amide II) cm^{-1};

δ_H (CDCl$_3$) 1.27 (3 H, d, J 6.8, -CH_3), 2.97 (1 H, t, J 5.3, -OH), 3.60 - 3.65 (1 H, m, -CHHOH or -NHCH-), 3.74 - 3.79 (1 H, m, -NHCH- or -CHHOH), 4.22 (5 H, s, C$_5H_5$), 4.36 (2 H, brs, Fc), 4.65 (1 H, brs, Fc), 4.68 (1 H, brs, Fc), 5.81 (1 H, brd, NH); δ_C {^{1}H} (CDCl$_3$) 17.29 (-CH_3), 47.76 (-NHCH-), 67.21, 68.11, 68.24 and 70.55 (x 2), 69.81 (C$_5H_5$), 75.63 (Fc - $ipso$), 171.2 (C=O); m/z (EI) 287 (M$^+$, 100%), 213 (67).

2-N-(1-Hydroxyethyl)ferrocenamide **8** isolated as a yellow crystalline solid after column chromatography (5% MeOH/CH$_2$Cl$_2$), yield = 80%.

m.p. 111-112.5 °C (Found: C, 57.34; H, 5.20; N, 5.00. C$_{13}$H$_{15}$FeNO$_2$ requires C, 57.17; H, 5.54; N, 5.13%); ν_{max} (nujol) 3340 (N-H), 3269 (O-H), 1627 (C=O amide I), 1552 (amide II) cm^{-1}; δ_H (CDCl$_3$) 2.82 (1 H, t, J 4.8, -OH), 3.56 (2 H, q, J 4.2, -NHCH_2-), 3.82 (2 H, q, J 4.8, -CH_2OH), 4.21 (5 H, s, C$_5H_5$), 4.37 (2 H, t, J 1.9, Fc), 4.68 (2 H, t, J 1.9, Fc), 6.14 (1 H, brs, -NH-); δ_C {^{1}H} (CDCl$_3$) 42.58 (-NHCH_2-), 62.74 (-OCH_2-), 68.18 (Fc x 2), 69.81 (C$_5H_5$), 70.57 (Fc x 2), 75.51 (Fc - $ipso$), 171.88 (C=O); m/z (EI) 273 (M$^+$, 91%), 121 (82), 56 (100).

Synthesis of ferrocenyloxazolines **9**, **10** *and* **11**.

The following method for the synthesis of (S)-2-ferrocenyl-4-(1-methylethyl)oxazoline **9** is representative.

To a light orange solution of (2S)-N-1-hydroxy-3-methylbutyl)ferrocenamide **6** (0.817 g, 2.59 mmol) and PPh$_3$ (2.49 g, 9.5 mmol) in acetonitrile (60 ml), was added NEt$_3$ (1.6 ml, 11.5 mmol) followed by CCl$_4$ (2.2 ml, 22.8 mmol) and the resultant solution stirred at room temperature under nitrogen overnight. After quenching with H$_2$O (80 ml) the reaction was extracted with petroleum ether (5 x 50 ml), the organics combined, dried (MgSO$_4$), filtered and evaporated. The crude product, which was contaminated by a substantial quantity of triphenylphosphine oxide, was purified by column chromatography (SiO$_2$ 40 - 63 µm, 30% EtOAc/40-60 petroleum ether) to give the pure ferrocenyl oxazoline as a dark yellow crystalline solid (0.685 g, 89%).

Note - Removing the solvent from the reaction mixture before work-up results in a substantial reduction in yield of the oxazoline.

m.p. 71.5-72.5 °C; [α]$_D^{22}$ -129 (c 1.5, EtOH); CD (CHCl$_3$) λ_{max} ($\Delta\varepsilon$) 464 (-0.80), 358 (+1.0) nm (Found: C, 64.46; H, 6.59; N, 4.59. C$_{16}$H$_{19}$FeNO requires C, 64.67; H, 6.44; N, 4.71%); ν_{max} (nujol) 1657 (C=N) cm^{-1}; δ_H (CDCl$_3$) 0.87 (3 H, d, J 6.8, -CH_3), 0.94 (3 H, d, J 6.8, -CH$_3$), 1.78 (1 H, hextet, J 6.6, -CH(CH$_3$)$_2$), 3.41 (1 H, q, J 7.0, -NCH-), 3.89 - 3.95 (1 H, m, -OCHH-), 4.00 (1 H, t, J 7.7, -OCHH-), 4.06 (5 H, s, C$_5H_5$), 4.26 (2 H, brs, Fc), 4.66 (1 H, brs, Fc), 4.70 (1 H, brs, Fc); δ_C {^{1}H} (CDCl$_3$) 17.79 (-CH_3), 18.81 (-CH_3), 32.27 (-CH(CH$_3$)$_2$), 68.92, 68.95, 69.27, 69.51 (C$_5H_5$), 70.06, 70.09, 70.60 (Fc - $ipso$), 72.27, 165.56 (C=N); m/z (EI) 297 (M$^+$, 100%), 254 (64), 211 (47), 121 (92).

Similarly prepared were:

(S)-2-ferrocenyl-4-methyloxazoline **10**. The work-up of this reaction differed slightly from above. After starting with **7** (0.78 g, 2.7 mmol) the reaction was quenched with H$_2$O (50 ml) and extracted with EtOAc (2 x 50 ml). The combined extracts were dried (MgSO$_4$), filtered and evaporated to give a dark crystalline residue. This was repeatedly triturated with petroleum ether (5 x 50 ml) and the resultant yellow solutions combined and evaporated. The remaining traces of Ph$_3$PO were removed by column chromatography (1 : 1 EtOAc/petroleum ether) to give **10** as a yellow crystalline solid, yield = 83%.

m.p. 84-85 °C; [α]$_D^{27}$ = -60 (c = 0.2, EtOH); CD (CHCl$_3$) λ_{max} ($\Delta\varepsilon$) 461 (+0.34), 336 (-0.25) nm (Found: C, 62.49; H, 5.83; N, 5.17. C$_{14}$H$_{15}$FeNO requires C, 62.48; H, 5.62; N, 5.20%); ν_{max} (nujol) 1651 (C=N) cm^{-1};

δ_H (CDCl$_3$) 1.32 (3 H, d, J 6.6, -CH_3), 3.86 (1 H, t, J 7.7, -OCHH-), 4.19 - 4.28 (1 H, m, -CHCH$_3$-), 4.19 (s, 5 H, C$_5$$H_5$), 4.33 (2 H, brs, Fc), 4.42 (1 H, dd, J 9.1, 8.0, -OCHH-), 4.75 (2 H, brs, Fc); δ_C {^{1}H} (CDCl$_3$) 21.57 (-CH$_3$), 61.80 (-CHCH$_3$-), 68.90, 68.98, 69.60 (C$_5$H$_5$), 70.20 (x 2), 73.66 (Fc - $ipso$), 165.81 (C=N); m/z (EI) 269 (M$^+$, 100%), 121 (95), 56 (55).

2-ferrocenyloxazoline **11**. Column chromatography (2-3% MeOH/CH$_2$Cl$_2$) failed to separate the product from Ph$_3$PO so the mixture was dissolved in CH$_2$Cl$_2$ and washed three times with an equal volume of aqueous 1M HCl. The combined aqueous layers were made basic with 1M NaOH and extracted with CH$_2$Cl$_2$. After drying (Na$_2$SO$_4$), filtration and evaporation, **11** was isolated as a yellow crystalline solid, yield = 77%.

m.p. 148-150 °C (Found: C, 61.38; H, 4.93; N, 5.55. C$_{13}$H$_{13}$FeNO requires C, 61.21; H, 5.14; N, 5.49%); ν_{max} (nujol) 1652 (C=N) cm^{-1}; δ_H (CDCl$_3$) 3.91 (2 H, t, J 9.4, -NCH_2-), 4.20 (5 H, s, C$_5$$H_5$), 4.34 (2 H, t, J 9.4, -OCH_2-), 4.34 (2 H, s, Fc), 4.74 (2 H, s, Fc); δ_C {^{1}H} (CDCl$_3$) 54.85 (-NCH$_2$-), 67.21 (-OCH$_2$-), 68.88 (Fc), 69.56 (C$_5$H$_5$), 70.17 (Fc), 166.98 (C=N); m/z 255 (M$^+$, 100%), 121 (82), 56 (73).

Synthesis of (S)-2-[(S)-2-(diphenylphosphino)ferrocenyl]-4-(1-methylethyl)oxazoline, (S)-(S)-^{i}Pr-Phosferrox **1**

A yellow/orange stirred solution of **9** (0.158 g, 0.53 mmol) and TMEDA (0.10 ml, 0.7 mmol) in Et$_2$O (6 ml) under nitrogen was cooled to -78 °C resulting in the formation of a yellow precipitate. To this was added dropwise *n*-BuLi (0.38 ml, 0.7 mmol), the reaction mixture darkening to red/brown. After stirring at -78 °C for 2 h. the Schlenk tube containing the orange non-homogeneous reaction mixture was transferred to an ice bath and stirring maintained for a further 5 min. To the resultant homogeneous orange-red solution was added PPh$_2$Cl (0.12 ml, 0.7 mmol) and the reaction mixture allowed to warm to room temperature. After 15 min. the reaction was quenched with sat. NaHCO$_3$ (10 ml) and diluted with ether (10 ml). The two layers were separated and the aqueous phase was extracted with Et$_2$O (10 ml). The organics were combined, dried (MgSO$_4$), filtered and evaporated to give and orange crystalline solid. This was purified by column chromatography (10% EtOAc/petroleum ether - preadsorbing on silica) to afford 0.163 g (64%) of a yellow/orange crystalline solid. Recrystallisation from hexane gave pure (S)-(S)-^{i}Pr-Phosferrox **1** as a single diastereoisomer.

m.p. 157-158 °C; [α]$_D$^{24} = +112 (c 0.1, EtOH); CD (CHCl$_3$) λ_{max} (Δε) 456 (+2.20), 368 (+0.49), 342 (-1.00), 315 (+2.16) nm (Found: C, 70.09; H, 6.11; N, 2.85. C$_{28}$H$_{28}$FeNOP requires C, 69.87; H, 5.86; N, 2.91%); ν_{max} (nujol) 1652 (C=N) cm^{-1}; δ_H (CDCl$_3$) 0.68 (3 H, d, J 7 Hz, -CH_3), 0.82 (3 H, d, J 7 Hz, -CH_3), 1.61-1.69 (1 H, m, -CH(CH$_3$)$_2$), 3.61 (1 H, brs, Fc), 3.67 (1 H, t, J 8 Hz, -OCHH-), 3.83-3.90 (1 H, m, -NCH-), 4.22 (5 H, s, C$_5$$H_5$), 4.22-4.30 (1 H, m, -OCHH-), 4.37 (1 H, brs, Fc), 4.99 (1 H, brs, Fc), 7.18 - 7.24 (5 H, m, Ph), 7.36 - 7.37 (3 H, m, Ph), 7.46 - 7.51 (2 H, m, Ph); δ_C {^{1}H} (CDCl$_3$) 17.52 (-CH$_3$), 18.61 (-CH$_3$), 32.05 (-CH(CH$_3$)$_2$), 69.57 (-OCH$_2$-), 70.72 (C$_5$H$_5$), 72.02, 72.14, 73.81, 73.85, 75.32 (d, J 16, Fc), 78.55 (d, J 15, Fc), 127.81 (Ph), 127.92 (Ph), 127.99 (Ph), 128.10 (Ph), 128.18 (Ph), 128.89 (Ph), 132.40 (d, J 20, Ph), 134.86 (d, J 22, Ph), 138.21 (d, J 13, Ph - $ipso$), 139.54 (d, J 12, Ph - $ipso$); δ_P (CDCl$_3$) -16.92; m/z (EI) 481 (M$^+$, 100%), 410 (68), 404 (44), 170 (38), 121 (76).

Synthesis of (S)-2-[(S)-2-(diphenylphosphino)ferrocenyl]-4-methyloxazoline, (S)-(S)-Me-Phosferrox **2**

A yellow/orange solution of **10** (0.162 g, 0.60 mmol) and TMEDA (0.12 ml, 0.8 mmol) in Et$_2$O (10 ml) under nitrogen was cooled to -78 °C resulting in the formation of a yellow precipitate. To this was added dropwise *n*-BuLi (0.36 ml, 0.8 mmol) causing the solution to darken and become homogeneous. After stirring at -78 °C

for 2 h. the Schlenk tube was transferred to an ice bath and stirred for a further 15 min. resulting in the formation of a precipitate. To this was added PPh2Cl (0.16 ml, 0.9 mmol) and after stirring for a further 15 min. the reaction was quenched with sat. NaHCO3. The two layers were separated, the aqueous phase washed with Et2O (10 ml), the organic phases combined, dried (MgSO4), filtered and evaporated. Column chromatography (40% EtOAc/petroleum ether) and recrystallisation (EtOAc/hexane) gave diastereomerially pure **2** as an orange crystalline solid (0.160 g, 59%).

m.p. 121-123 °C; $[\alpha]_D^{21}$ +140 (c = 0.2, EtOH); CD (CHCl3) λ_{max} ($\Delta\varepsilon$) 456 (+5.92), 365 (+1.06), 344 (-1.47), 314 (+9.07) nm (Found: C, 69.02; H, 5.18; N, 2.87. C26H24FeNOP requires C, 68.89; H, 5.34; N, 3.09%); ν_{max} (nujol) 1657 (C=N) cm^{-1}; δ_H (CDCl3) 1.13 (3 H, d, J 6.6, -CH3), 3.39 (1 H, t, J 8.1, -OCHH-), 3.64 (1 H, brs, Fc), 4.12 (1 H, hextet, J 8, -CHCH3-), 4.23 (5 H, s, C5H5), 4.41 (1 H, brs, Fc), 4.41 - 4.45 (1 H, m, -OCHH-), 5.05 (1 H, brs, Fc), 7.18 - 7.26 (5 H, m, Ph), 7.37 - 7.38 (3 H, m, Ph), 7.47 - 7.49 (2 H, m, Ph); δ_C {^{1}H} (CDCl3) 21.14 (-CH3), 61.51 (-CHCH3-), 70.79 (C5H5), 70.93, 72.13, 73.95 (x2?), 74.90 (d, J 16, Fc), 78.40 (d, J 14, Fc), 127.89 (Ph), 127.98 (Ph), 128.05 (Ph), 128.17 (Ph), 128.25 (Ph), 128.43 (Ph), 129.02 (Ph), 132.29 (d, J 20, Ph), 134.86 (d, J 22, Ph), 137.96 (d, J 14, Ph - *ipso*), 139.44 (d, J 13, Ph - *ipso*), 165.82 (C=N); δ_P (CDCl3) -16.67; *m/z* (EI) 453 (M$^+$, 89%), 410 (51), 121 (100).

Synthesis of (S)-2-[(S)-2-(trimethylsilyl)ferrocenyl]-4-(1-methylethyl)oxazoline **12**

A solution of **9** (0.252 g, 0.85 mmol) and TMEDA (0.17 ml, 1.1 mmol) in Et2O (8 ml) was lithiated as described in the synthesis of **1**. After stirring at 0 °C for 15 min., TMSCl (0.14 ml, 1.1 mmol) was added and after stirring at room temperature for a further 15 min. the reaction was quenched with NaHCO3 (10 ml). The reaction mixture was worked up as described for **1** and the crude product examined by ^{1}H NMR spectroscopy which revealed an approximately 100 : 1 ratio of diastereoisomers by comparison of the multiplet centred at 4.89 ppm (major isomer) with that at 4.92 ppm.[11a] Column chromatography (10% EtOAc/petroleum ether) gave **12** as an orange crystalline solid (0.297 g, 95%).

m.p. 38.7 - 39.9 °C; $[\alpha]_D^{20}$ = +286 (c = 0.2, EtOH) (Found: C, 61.96; H, 7.59; N, 3.90. C19H27FeNOSi requires C, 61.78; H, 7.37; N, 3.79%); ν_{max} (CHCl3) 1654 (C=N) cm^{-1}; δ_H (CDCl3) 0.31 (9 H, s, -Si(CH3)3), 0.92 (3 H, d, J 6.7, -CH3), 1.02 (3 H, d, J 6.7, -CH3), 1.81 (1 H, octet, J 6.5, -CH(CH3)2), 3.91 - 4.03 (2 H, m, -OCHHCH-), 4.18 (5 H, s, C5H5), 4.25 - 4.28 (2 H, m, -OCHH- and Fc), 4.43 (1 H, t, J 2.4, Fc), 4.89 - 4.90 (1 H, m, Fc); δ_C {^{1}H} (CDCl3) 0.5 (-Si(CH3)3), 18.04 (-CH3), 19.12 (-CH3), 32.57 (-CH(CH3)2), 69.35 (-OCH2-), 69.46 (C5H5), 71.55, 72.84, 73.00, 73.18, 75.36, 165.77 (C=N); *m/z* (EI) 369 (M$^+$, 77%), 354 (76), 121 (100).

Synthesis of (S)-2-[(S)-2-(trimethylsilyl)ferrocenyl-4-methyloxazoline **13**

A solution of **10** (0.606 g, 2.25 mmol) and TMEDA (0.44 ml, 2.9 mmol) in Et2O (17 ml) was lithiated and treated with TMSCl (0.37 ml, 2.9 mmol)as described above. The crude reaction mixture was found to contain a greater than 50 : 1 ratio of isomers by comparison of the multiplet centred at 4.92 ppm (major isomer) with that at 4.97 ppm in the ^{1}H NMR spectrum. After column chromatography (20% EtOAc/petroleum ether) the product was isolated as a yellow crystalline solid (0.557 g, 72%).

m.p. 61 - 62 °C; $[\alpha]_D^{26}$ = +406 (c 0.2, EtOH) (Found: C, 59.85; H, 6.95; N, 4.04. C17H23FeNOSi requires C, 59.82; H, 6.79; N, 4.10%); ν_{max} (nujol) 1651 (C=N) cm^{-1}; δ_H (CDCl3) 0.30 (s, 9 H, -Si(CH3)3), 1.29 (3 H, d, J 6.5, -CHCH3), 3.86 (1 H, d, J 8, -OCHH-), 4.19 (5 H, s, C5H5), 4.19 - 4.27 (1 H, m, -CHCH3-), 4.27 (1 H, brs, Fc), 4.39 (1 H, t, J 8, -OCHH-), 4.46 (1 H, brs, Fc), 4.95 (1 H, brs, Fc); δ_C {^{1}H} (CDCl3) 0.5 (-Si(CH3)3),

21.53 (-CH_3), 61.94 (-$CHCH_3$-), 69.53 (C_5H_5), 71.73, 73.10, 73.19, 73.44, 75.17, 165.98 (C=N); m/z (EI) 341 (M$^+$, 97%), 326 (58), 121 (100).

Synthesis of (S)-2-[(R)-2-(diphenylphosphino)-5-(trimethylsilyl)ferrocenyl]-4-(1-methylethyl)oxazoline **14**

Route A. A light orange solution of **12** (0.216 g, 0.58 mmol) in THF (4 ml) at -78 °C was treated with n-BuLi (0.37 ml, 0.76 mmol) causing the reaction mixture to darken. After stirring for 2 h. the reaction mixture was allowed to warm to 0 °C and stirred for a further 5 min. resulting in further darkening. To this was added PPh$_2$Cl (0.14 ml, 0.8 mmol) and after stirring at room temperature for 0.5 h. the reaction was quenched with NaHCO$_3$ (10 ml). The layers were separated and the aqueous phase washed with Et$_2$O (10 ml), the organics combined, dried (MgSO$_4$), filtered and evaporated *in vacuo*. Column chromatography (20%EtOAc/petroleum ether) gave **14** as a dark orange oil (0.151 g, 47%).

Route B. A solution of **9** (0.209 g, 0.70 mmol) and TMEDA (0.13 ml, 0.9 mmol) in Et$_2$O (8 ml) was lithiated and treated with TMSCl (0.12 ml, 0.9 mmol) as described for the synthesis of **12**. After warming to room temperature, additional Et$_2$O (3 ml) and TMEDA (0.13 ml, 0.9 mmol) were added and the reaction mixture cooled to -78 °C. After dropwise addition of n-BuLi (0.50 ml, 0.9 mmol), the reaction was stirred at -78 °C for 2 h. followed by 0.5 h. at 0 °C. To the resultant dark orange solution was added PPh$_2$Cl (0.16 ml, 0.9 mmol) and the reaction mixture stirred at room temperature for 0.5 h. before quenching with NaHCO$_3$ (10 ml). Work up as described for route A gave **14** as a dark orange oil (0.292 g, 75%).

m.p. 105.5 - 107 °C (hexane); $[\alpha]_D^{21}$ = +134 (c = 0.2, EtOH) (Found: C, 67.13; H, 6.44; N, 2.37. C$_{31}$H$_{36}$FeNOPSi requires C, 67.27; H, 6.56; N, 2.53%); ν_{max} (CHCl$_3$) 1647 (C=N) cm^{-1}; δ_H (CDCl$_3$) 0.29 (9 H, s, -Si(CH_3)$_3$), 0.55 (3 H, d, J 6.7, -CH_3), 0.63 (3 H, d, J 6.7, -CH_3), 1.44 (1 H, octet, J 6.6, -CH(CH$_3$)$_2$), 3.71 - 3.72 (1 H, m, Fc), 3.79 - 4.00 (3 H, m, -OCH_2CH-), 4.16 (5 H, s, C$_5H_5$), 4.26 (1 H, d, J 2.5, Fc), 7.15 - 7.20 (5 H, m, Ph), 7.34 - 7.35 (3 H, m, Ph), 7.48 - 7.52 (2 H, m, Ph); δ_C {^{1}H} (CDCl$_3$) 0.5 (-Si(CH_3)$_3$), 17.86 (-CH_3), 18.31 (-CH_3), 32.58 (-CH(CH$_3$)$_2$), 69.24 (-OCH_2-), 70.68 (C$_5H_5$), 72.57, 75.79, 75.82, 77.13, 79.69 (d, J 15, Fc), 81.69 (d, J 14, Fc), 127.51, 127.79, 127.86, 128.05, 128.12, 128.86, 132.21 (d, J 19, Ph), 135.26 (d, J 22, Ph), 139.02 (d, J 14, Ph - *ipso*), 139.82 (d, J 12, Ph - *ipso*), 164.85 (C=N); m/z (EI) 553 (M$^+$, 66%), 482 (36), 121 (65), 73 (100).

Synthesis of (S)-2-[(R)-2-(diphenylphosphino)-5-(trimethylsilyl)ferrocenyl]-4-methyloxazoline **15**

Route A. Starting with **13** (0.216 g, 0.63 mmol), repetition of route A above and column chromatography (5% EtOAc/petroleum ether) gave **15** (0.205 g, 62%) as a dark orange oil.

Route B. A solution of **10** (0.335 g, 1.24 mmol) and TMEDA (0.24 ml, 1.6 mmol) in Et$_2$O (10 ml) was lithiated and treated with TMSCl (0.21 ml, 1.7 mmol) as described above for the synthesis of **13**. After warming to room temperature, addition of THF (10 ml) gave an orange homogeneous solution which was cooled to -78 °C. After dropwise addition of n-BuLi (0.78 ml, 1.6 mmol), the darkened reaction mixture was stirred at -78 °C for 2 h. followed by 5 min. at 0 °C. To this was added PPh$_2$Cl (0.29 ml, 1.6 mmol) and the reaction mixture stirred at room temperature for 0.5 h. before quenching with NaHCO$_3$ (10 ml). Standard work up and column chromatography (10% EtOAc/petroleum ether) gave **15** as a dark orange oil (0.495 g, 76%).

$[\alpha]_D^{22}$ = +32 (c = 0.2, EtOH) (Found: C, 66.40; H, 6.38; N, 2.49. C$_{29}$H$_{32}$FeNOPSi requires C, 66.29; H, 6.14; N, 2.67%); ν_{max} (nujol) (C=N) 1650 cm^{-1}; δ_H (CDCl$_3$) 0.30 (9 H, s, -Si(CH_3)$_3$), 0.81 (3 H, d, J 6.6,

-CHCH_3), 3.71 (1 H, d, J 2.5, Fc), 3.72 (1 H, dd, J 8, 5.5, -OCHH-), 3.96 (1 H, t, J 8.5, -OCHH-), 4.05 - 4.11 (1 H, m, -CHCH$_3$-), 4.20 (5 H, s, C$_5$H$_5$), 4.25 (1 H, d, J 2.4, Fc), 7.20 - 7.23 (5 H, m, Ph), 7.35 - 7.37 (3 H, m, Ph), 7.49 - 7.51 (2 H, m, Ph); δ_C {^{1}H} (CDCl$_3$) 1.0 (-Si(CH$_3$)$_3$), 22.62 (-CHCH$_3$), 61.87 (-CHCH$_3$), 70.92 (C$_5$H$_5$), 73.00 (-OCH$_2$-), 75.56 (Fc), 80.11 (d, J 14, Fc), 82.33 (d, J 14, Fc), 127.69 (Ph), 127.89 (Ph), 127.96 (Ph), 128.13 (Ph), 128.21 (Ph), 128.87 (Ph), 132.30 (d, J 19, Ph), 135.02 (d, J 22, Ph), 138.71 (d, J 14, Ph - *ipso*), 139.52 (d, J 13, Ph - *ipso*), 164.83 (C=N); *m/z* (EI) 525 (M$^+$, 82%), 482 (40), 121 (100).

Synthesis of (S)-2-[(R)-2-(diphenylphosphino)ferrocenyl]-4-(1-methylethyl)oxazoline, (S)-(R)-^{i}Pr-Phosferrox **3**

A yellow solution of 1 M TBAF in THF (10 ml) containing approximately 5% H$_2$O and **14** (0.138 g, 0.25 mmol) was heated at reflux for 4h. The resultant orange solution was evaporated *in vacuo* to low volume and partitioned between Et$_2$O (10 ml) and H$_2$O (10 ml). After separation, the aqueous phase was further extracted with Et$_2$O and the organics combined, dried (MgSO$_4$), filtered and evaporated *in vacuo*. The resultant yellow residue was column chromatographed (10% EtOAc/40-60 petroleum ether) to give (S)-2-[(R)-2-diphenylphosphino)ferrocenyl]-4-(1-methylethyl)oxazoline **3** as a yellow crystalline solid (0.090 g, 75%).
m.p. 132-132.5 °C; $[\alpha]_D^{20}$ = -53 (*c* 0.15, EtOH); CD (CHCl$_3$) λ_{max} ($\Delta\epsilon$) 492 (+0.45), 434 (-0.43), 361 (-0.31), 344 (+0.35), 314 (-2.38) nm (Found: C, 69.60; H, 5.90; N, 2.85. C$_{28}$H$_{28}$FeNOP requires C, 69.87; H, 5.86; N, 2.91%); ν_{max} (nujol) 1660 (C=N) cm^{-1}; δ_H (CDCl$_3$) 0.63 (3 H, d, J 7 Hz, -CH$_3$), 0.65 (3 H, d, J 7 Hz, -CH$_3$), 1.50-1.58 (1 H, m, -CH(CH$_3$)$_2$), 3.62 (1 H, brs, Fc), 3.89-4.08 (3 H, m, -OCH$_2$CH-), 4.22 (5 H, s, C$_5$H$_5$), 4.36 (1 H, brs, Fc), 4.94 (1 H, brs, Fc), 7.19-7.23 (5 H, m, Ph), 7.35-7.37 (3 H, m, Ph), 7.48-7.53 (2 H, m, Ph); δ_C {^{1}H} (CDCl$_3$) 17.88 (-CH$_3$), 32.44 (-CH$_3$), 69.47 (-OCH$_2$-), 70.44, 70.67 (C$_5$H$_5$), 72.09, 72.41, 74.07, 74.95 (d, J 16, Fc), 78.12 (d, J 14, Fc), 127.71 (Ph), 127.83 (Ph), 127.90 (Ph), 128.07 (Ph), 128.15 (Ph), 128.55 (Ph), 128.86 (Ph), 132.38 (d, J 19, Ph), 134.98 (d, J 22, Ph), 138.31 (d, J 13, Ph - *ipso*), 139.37 (d, J 12, Ph - *ipso*), 164.62 (C=N); δ_P (CDCl$_3$) -18.03; *m/z* (EI) 481 (M$^+$, 32%), 410 (19), 170 (22), 121 (100).

Synthesis of (S)-2-[(R)-2-(diphenylphosphino)ferrocenyl]-4-methyloxazoline, (S)-(R)-Me-Phosferrox **4**
Starting with **15** (0.202 g, 0.38 mmol), TBAF mediated desilylation as described above and column chromatography (40% EtOAc/petroleum ether) gave **4** (0.157 g, 90%) as a yellow crystalline solid.
m.p. 169-170.5 °C; $[\alpha]_D^{22}$ = -144 (*c* 0.2 EtOH); CD (CHCl$_3$) λ_{max} ($\Delta\epsilon$) 452 (-1.52), 365 (-0.62), 344 (+0.60), 306 (-10.00) nm (Found: C, 69.27; H, 5.38; N, 2.92. C$_{26}$H$_{24}$FeNOP requires C, 68.89; H, 5.34; N, 3.09%); ν_{max} (nujol) 1656 (C=N) cm^{-1}; δ_H (CDCl$_3$) 1.04 (3 H, d, J 6.3, -CH$_3$), 3.64 (1 H, brs, Fc), 3.83 (1 H, td, J 5, 2, -OCHH-), 4.07 - 4.13 (2 H, m, -OCHHCHCH$_3$-), 4.21 (5 H, s, C$_5$H$_5$), 4.38 (1 H, t, J 2.5, Fc), 4.98 (1 H, brs, Fc), 7.18 - 7.24 (5 H, m, Ph), 7.36 - 7.38 (3 H, m, Ph), 7.49 - 7.53 (2 H, m, Ph); δ_C {^{1}H} (CDCl$_3$) 21.34 (-CH$_3$), 61.53 (-CHCH$_3$-), 70.84 (C$_5$H$_5$), 71.34, 72.46, 73.58, 74.11, 127.76 (Ph), 127.86 (Ph), 127.92 (Ph), 127.99 (Ph), 128.14 (Ph), 128.21 (Ph), 128.96 (Ph), 132.35 (d, J 19, Ph), 134.98 (d, J 21, Ph), 138.10 (d, J 13, Ph - *ipso*), 139.40 (d, J 12, Ph - *ipso*); δ_P (CDCl$_3$) -17.44; *m/z* (EI) 453 (M$^+$, 100%), 410 (90), 121 (66).

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