

Another side of the oxazaphospholidine oxide chiral *ortho*-directing group†Nelson Martins,^{a,b} Nuno Mateus,^a Daniele Vinci,^a Ourida Saidi,^a Amadeu Brigas,^{*b} John Bacsá^a and Jianliang Xiao^{*a}

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A new ferrocenyl oxazaphospholidine oxide **3** was synthesized together with its P-epimer **2** in the reaction of ferrocene lithium with phosphoramidite chloride **1**. **3** was successfully derivatized into planar chiral 1,2-ferrocenes, including phosphine ligands, *via* highly diastereoselective *ortho*-lithiation and subsequent functionalization; these compounds display opposite planar chirality to those obtained from **2**. Some of these 1,2-ferrocenes were further lithiated, allowing for the introduction of a free phosphine group at the oxazaphospholidine ring. The X-ray structures of the compounds **2** and **3** as well as those of the new 1,2-ferrocenes **4** and **7** have been determined.

Introduction

Since the last two decades there has been an ever increasing demand for pure optically active substances.^{1–3} Concurrently asymmetric catalysis has gained pre-eminence in asymmetric synthesis,^{4,5} prompting the pursuit of effective chiral ligand design.⁴ In this context, the development of new families of chiral ligands in a modular fashion is particularly advantageous, because it allows for fine-tuning of the ligand's steric and electronic properties.^{4,6,7}

Due to its unique attractive characteristics, ferrocene has arisen as a widespread scaffold for the preparation of chiral ligands, which have irrefutably proven remarkably successful in asymmetric catalysis.^{8–10} Among ferrocenyl ligands, planar chiral 1,2-disubstituted ones emerge as the most prolific, and are often built by sequential, diastereoselective, directed *ortho*-metalation (*DoM*) and functionalization of ferrocenes containing a chiral *ortho*-directing group (CDG).^{8,11–20} Ideally, following diastereoselective abstraction of the desired cyclopentadienyl hydrogen and *ipso*-substitution by a new group, such CDGs should allow further transformation into new desirable structures. Indeed several known CDGs allow further transformations, giving rise to a variety of planar chiral ferrocenes.^{8,10,18,21}

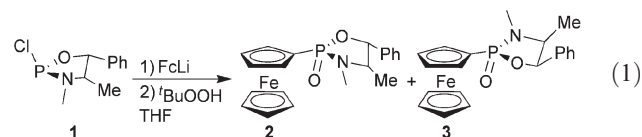
In a previous paper, we reported the highly diastereoselective *ortho*-lithiation of (2*R*,4*S*,5*R*)-3,4-dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]oxazaphospholidine 2-oxide (**2**), which was

exploited for the synthesis of 1,2-planar chiral ferrocenes, including phosphines.²² We also showed that these ferrocenyl phosphine-oxazaphospholidine oxide ligands are viable for the Suzuki–Miyaura coupling reactions.²³ Herein we wish to present further aspects of the oxazaphospholidine-oxide moiety, which can act as a CDG to give rise to configurationally opposite planar chiral compounds.

Results and discussion

Synthesis of (2*S*,4*S*,5*R*)-3,4-dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]oxazaphospholidine 2-oxide (**3**)

In the presence of *N*-methylmorpholine, the phosphoramidite chloride **1** was prepared from ephedrine and PCl_3 .^{22,24–26} A slight modification on the filtration step improved the yield to 93%.²² Aiming to prepare compound **2** *via* our previously presented procedure,²² the chloride **1** was submitted to nucleophilic displacement with ferrocenyl lithium (FcLi) (eqn (1)). However, in addition to the desired product, the diastereomer **3** was also observed. This is interesting, since **3** is the P-epimer of **2**, and could allow access to derivatives of opposite planar chirality to those from **2**. A few repetitions of this synthesis were therefore performed, and we noticed a variation in the ratio between **2** and **3**, from one occasion to another. After some investigation, it was found that temperature plays a key role. This is illustrated by the experiments below.



Two parallel reactions were undertaken under similar conditions except for the temperature. First, ferrocene was lithiated

^aDepartment of Chemistry, University of Liverpool, Liverpool L69 7ZD, UK. E-mail: j.xiao@liv.ac.uk; Fax: +44 (0)151 7943588; Tel: +44 (0) 151 7942937

^bCIQA, Departamento de Química e Farmácia, Faculdade de Ciências e Tecnologia, Universidade do Algarve, Campus de Gambelas, 8005-139 Faro, Portugal. E-mail: abrigas@ualg.pt; Fax: +351 289 8000066; Tel: +351 289 800900 – ext 7639

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with t BuLi to form FcLi in the presence of t BuOK. A fine red-brick precipitate was formed and the slurry cooled to -78 °C before being equally divided *via* syringe and added into two identical THF solutions of oxazaphospholidine chloride **1**. One of the solutions (A) of **1** had previously been cooled to -78 °C, and was then allowed to slowly reach room temperature upon addition of FcLi. In contrast, the other solution (B) had been at room temperature before the introduction of FcLi. Following overnight stirring, both mixtures were cooled from ambient temperature to 0 °C and oxidized with t BuOOH. Aqueous work-up and flash chromatography purification allowed the ready separation of (2*R*,4*S*,5*R*)-3,4-dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide **2** from its new P-epimer (2*S*,4*S*,5*R*)-3,4-dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]-oxazaphospholidine 2-oxide **3**. Both reactions resulted in similar overall yields, 65% from the reaction A and 62% from B. However the ratio between compounds **2** and **3** varied, from 5 : 2 in the first case to 2 : 3 in the second. Since the reaction conditions such as solvent, reaction time and the reagent concentrations did not vary from one reaction to the other, the results suggest that **2** is favoured by lower temperature whereas **3** is favoured by high temperature. Thus, the pathway leading to **3** is energetically less favourable. The structures of both **2** and **3** have been determined by X-ray diffraction, and are shown in Fig. 1 and 2.

Compounds **2** and **3** are diastereomers with inverted configuration at the phosphorus, *i.e.* they are P-epimers, with **2** being *R* and **3** being *S* configured at the phosphorus atom. As quasi-enantiomers, they are mirror images of each other if the ephedrine backbone is ignored. In compound **2** the P=O bond is *anti* relative to the CHPh proton from the oxazaphospholidine ring, resulting in P–H coupling. Thus, its 1 H NMR displays a triplet corresponding to the CHPh proton, which also couples with the CHMe moiety, with $^3J_{\text{PH}} = J_{\text{HH}} = 6.7$ Hz. Conversely, in the new P-epimer **3**, the P=O bond is *syn* to the CHPh proton, and consequently, P–H coupling does not occur; only a doublet is observed for the CHPh proton in the 1 H NMR, with, $J_{\text{HH}} =$

6.1 Hz. Its CHPh proton also appears more acidic than the one in **2**, 5.88 vs. 5.47 ppm. Such behaviour is typical of oxazaphospholidines.^{27,28}

Both epimers adopt an envelop conformation. The flap atom, the CHPh carbon, is out of the plane formed by O1–P1–N2–C12, in Fig. 1, and O1–P2–N3–C4, in Fig. 2. The N methyl group from both epimers is pseudo-equatorial relative to the oxazaphospholidine ring, and parallel to the ferrocene backbone. Flanked by these last two groups, the P=O is pointing down being half the distance between the substituted Cp ring and the iron atom. The methyl group of the CHMe unit is pseudo-axial, while the CHPh phenyl is pseudo-equatorial. In compound **2** the flap is towards the ferrocene moiety while the CHMe methyl points away from it. In contrast, compound **3** presents the flap away from the ferrocene; but the CHMe methyl is toward it. In both compounds, the CHPh phenyl substituent is close to being perpendicular to the substituted Cp ring.

Exocyclic chloride displacement at **1** by carbon-based nucleophiles has been said to involve overall retention of configuration at the phosphorus atom.^{29,30} Such has also been the case for P(III) oxidations.^{31–34} However, ^{31}P NMR analysis of our reaction revealed the presence of both P-epimers prior to the oxidation, with little ratio variation after its occurrence. A possible explanation for this epimerization is that the nucleophilic displacement may proceed *via* two pathways with different activation energies.²² The one leading to **2** has a lower barrier than the one for **3**; hence a higher temperature promotes the formation of **3** while a low temperature gives favour to **2**. The presence of nucleophilic impurities, such as water, alcohols and amines, could also accelerate the epimerization.^{35,36} In addition, some oxazaphospholidines are known to undergo epimerization.^{27,29,32,35,36}

Stereoselective *ortho*-lithiation of **3**

Obtaining **3** raised the question whether the CDG could be effectively used for the deprotonation of ferrocene, and in particular, whether it would lead to the formation of optically active

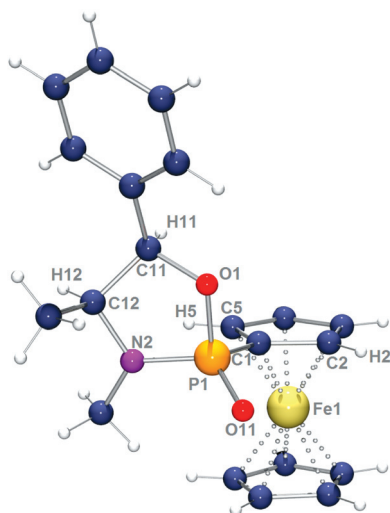


Fig. 1 X-ray structure of **2**. Selected bond lengths (Å) and angles (°): P1–C1 1.7710 (16), P1–O1 1.6054 (12), P1–O11 1.4675 (14), P1–N2 1.6375 (14), O1–P1–N2 94.82 (7), O11–P1–N2, 119.67 (8), O11–P1–O1 112.61 (8), O11–P1–C1 112.61 (8), N2–P1–C1 109.39 (8).

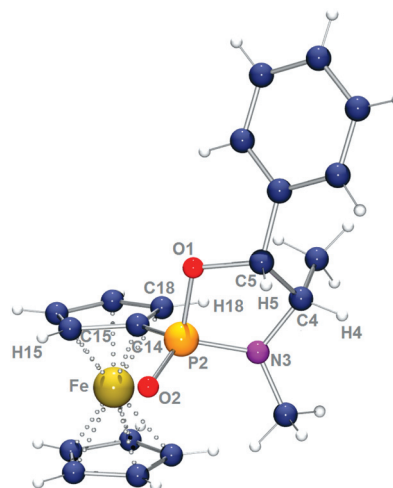
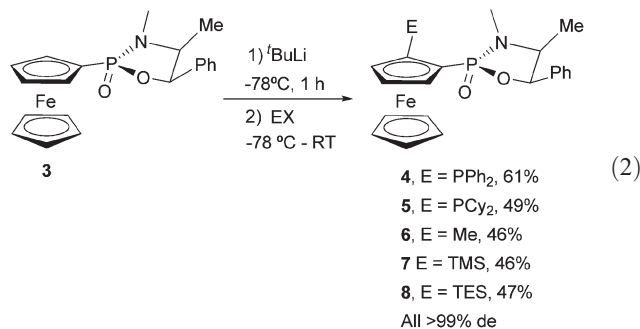


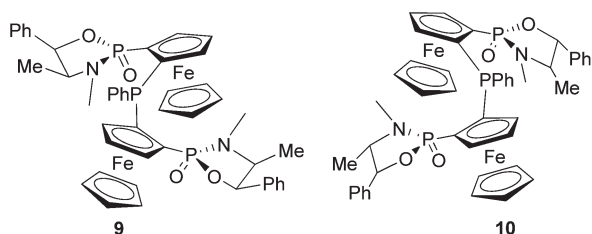
Fig. 2 X-ray structure of **3**. Selected bond lengths (Å) and angles (°): P2–C14 1.7663 (16), P2–O1 1.6085 (11), P2–O2 1.4753 (11), P2–N3 1.6509 (13), O1–P2–N3 95.16 (6), O2–P2–N3, 117.33 (7), O2–P2–O1 116.01, O2–P2–C14 111.86 (7), N3–P2–C14 110.74 (7).

ferrocenes with opposite planar chirality to those derived from the P-epimer **2**. It is important to notice that the somewhat different steric and electronic properties of **3** vs. **2**, for instance their CHPh proton acidity, could lead to different results. In fact, the presence of acidic protons in a supposedly potential CDG has led to unexpected reactions before,³⁷ and the same has been noted in a ferrocenyl imidazoline containing a CHPh proton.³⁸

According to our previous method,²² **3** was lithiated with ^tBuLi at $-78\text{ }^{\circ}\text{C}$ followed by quenching with an electrophile EX (eqn (2)). Planar chiral 1,2-ferrocenes **4–8** were indeed obtained with very high regio and diastereo-selectivity, >99%. Similar to compound **2**,²² the new P-epimer was compatible with several different electrophiles, as seen from **4–8**, and there was no diastereoselectivity-dependence on the electrophiles used.



Interestingly, when dichlorophenylphosphine PCl_2Ph and two equivalents of **3** or **2** were used, the reaction resulted in the formation of the corresponding diferrocenes **9** or **10**, in 57 and 66% yield, respectively. In the ^{31}P NMR spectra, the phosphine of **9** and **10** appears as singlet at -37.2 and -38.8 ppm, respectively.



In order to infer the planar chiral configuration at the new 1,2-ferrocenes, crystals of **4** and **7** were grown and analysed by X-ray diffraction. The structures are presented in Fig. 3 and 4, showing that both **4** and **7** present S_p configuration at the chiral plane. The most significant change in the structure on going from **3** to **4** and **7** is that the bi-ring moiety constituted of the oxazaphospholidine oxide and its phenyl substituent is more or less parallel to the substituted Cp ring in **4** and **7**, whereas this relationship is close to being perpendicular in **3**.

Apparently, P–C bond rotation took place during the formation of these 1,2-substituted ferrocenes, presumably driven by steric effect, as lithiation at C15 of **3** would afford a compound with more congested substituents. This rotation can be seen in the torsion angle of N3–P2–C14–C18 being -18.73 in **3** and that of N1–P1–C11–C12 being 117.18 in **4**.

The X-ray structures thus confirm that the new P-epimer **3** directs the *ortho*-lithiation on the ‘opposite side’ when compared with **2**, at C18 in Fig. 2 vs. C5 in Fig. 1. This is what one would expect, considering that **3** and **2** are quasi-enantiomers. A door is

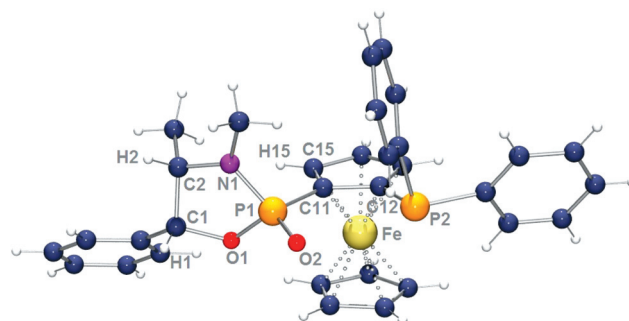


Fig. 3 X-ray structure of **4**. Selected bond lengths (Å) and angles ($^{\circ}$): P1–C11 1.786 (2), P1–O1 1.6093 (16), P1–O2 1.4639 (16), P1–N1 1.643 (2), P2–C12 1.829 (2), O1–P1–N1 94.41 (9), O2–P1–N1 115.58 (9), O2–P1–O1 118.32 (9), O2–P1–C11 110.71 (10), N1–P1–C11 112.87 (10), P2–C12–C11 125.14 (15), P1–C11–C12 126.91 (16).

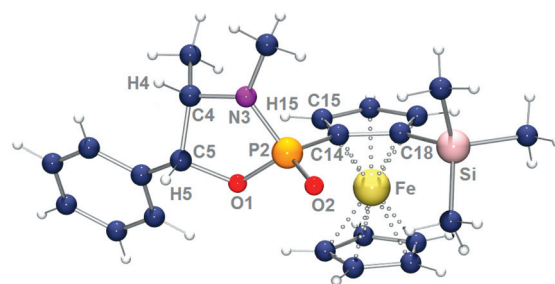
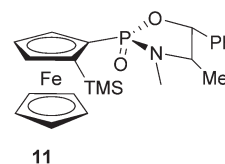


Fig. 4 X-ray structure of **7**. Selected bond lengths (Å) and angles ($^{\circ}$): P2–C14 1.778 (2), P2–O1 1.6054 (18), P2–O2 1.465 (2), P2–N3 1.649 (2), Si–C18 1.879 (3), O1–P2–N3 94.61 (10), O2–P2–N3 114.79 (12), O2–P2–O1 118.39 (11), O2–P2–C14 111.96 (11), N3–P2–C14 112.97 (12), P2–C14–C18 128.9 (2), Si–C18–C14 131.5 (2).

thus opened for the synthesis of new (S_p)-1,2-ferrocenyl oxazaphospholidine oxides, complementing the previous work that leads to the (R,R_p) diastereomers.²²

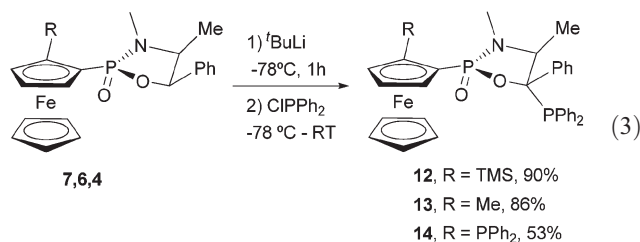
Further transformation of 1,2-ferrocenyl oxazaphospholidine oxides

The presence of the oxazaphospholidine oxide CDG presents further opportunities for lithiation and reaction with electrophiles. Aiming to synthesize ferrocenyl oxazaphospholidines with (R,S_p) and (S,R_p) configurations, we decided to perform a second lithiation at our (S,S_p) and (R,R_p) diastereomers containing a dummy TMS group, *i.e.* compounds **7** and **11**, respectively. This would permit lithiation at the other cyclopentadienyl proton, *ortho* to the CDG, first leading to 1,2,3-substituted ferrocenes and then to the desired 1,2-ferrocenes upon TMS removal.³⁹ Compound **11** was prepared from **2**.²²



In a similar set of conditions to those used for the lithiation of **3**, we reacted **11** with ^tBuLi, surprisingly obtaining a mixture of

compounds which contained mostly the starting material. In stark contrast, reacting **7** with the lithiating agent afforded a new product (**12**) in high yield (eqn (3)). However, the ^{31}P and ^1H NMR data, including COSY NMR, revealed that it was the CHPh proton at the heterocyclic ring that was abstracted, not the initially targeted cyclopentadienyl one. Reaction with **6** and **4** demonstrated the same type of behaviour, affording ligands **13** and **14**.



Due to their relative position, the oxazaphospholidine phosphorus and the new diphenylphosphine phosphorus in products **12** to **14** display P–P coupling with each other, with their J_{PP} constants ranging from 75.3 to 83.2 Hz. Interestingly, the new group presents a rather unusual down-field chemical shift for a free phosphine, from 46 to 48 ppm, which may stem from the deshielding effect of the vicinal phenyl group.

The higher propensity of **4**, **6** and **7** to undergo CHPh proton abstraction than **11** is likely a result of several factors. Fig. 3 and 4 show that the CHPh proton and the P=O bond are *cis* positioned. Thus, abstraction of this proton would be facilitated by the phosphoryl oxygen. Lithiation at the H15-bound C15 requires rotation of the C–P bond, as indicated by Fig. 3 and 4; but this may become less likely due to the presence of the newly introduced neighbouring group, and would result in sterically more demanding 1,2,3-substituted ferrocenes. In addition, the CHPh proton in **3** and its derivatives appears more acidic than that in **2** and its derivatives.

This different reactivity between diastereomers also explains why we have observed a tendency to obtain lower product yields when derivatizing **3** than when using **2**. In one instance, while lithiating and quenching **3** with PClPh_2 , we obtained 54% of **4** in addition to 25% of **14**. This bis-lithiation can be minimized or augmented by reducing or increasing the amount of $t\text{-BuLi}$ used.

Conclusions

The synthesis, highly stereoselective *ortho*-lithiation and functionalization of **3** has led to the establishment of a new family branch of ferrocenyl oxazaphospholidine oxides, namely (*S,S_p*)-1,2-ferrocenes. Using its diastereomer **2**, the corresponding (*R,R_p*)-compounds can be accessed. Chemical dissimilarities between **3** and **2**, and between their derivatives, led to different reactivity, favouring substitution of the CHPh proton in the (*S,S_p*)-1,2-ferrocenes instead of the (*R,R_p*) diastereomers. Along with our previous study, these results demonstrate that the oxazaphospholidine-oxide is a versatile CDG, allowing for the synthesis of a range of substituted chiral ferrocenes, including ligands of opposite planar chirality.

Experimental section

General conditions

All reactions were carried out under a nitrogen atmosphere with standard Schlenk techniques. All solvents were dried before use. Flash-chromatography was performed using silica gel 60 Å (37–70 nm). Analytical TLC was carried out utilizing 0.25 mm pre-coated plates (silica gel 60 UV254). For NMR spectra, samples were dissolved in CDCl_3 and run at room temperature. ^1H (400 MHz), ^{13}C (100 MHz), and ^{31}P (162 MHz) NMR spectra were recorded on a 400 MHz Bruker spectrometer. Mass spectra were measured at 50 eV (EI). Elemental analysis was performed by the Microanalysis Laboratory, Department of Chemistry, University of Liverpool. Melting points are reported as their uncorrected values.

Synthesis of oxazaphospholidines

(2*R*,4*S*,5*R*)-2-Chloro-3,4-dimethyl-5-phenyl-[1,3,2]oxazaphospholidine (1). A 1 L Schlenk flask was charged with toluene (250 mL) and *N*-methylmorpholine (26.6 mL, 242.0 mmol). PCl_3 (10.5 mL, 121 mmol) was added and the mixture cooled to -78°C . A second Schlenk flask was charged with (*1*R*,2*S**)-(-)-ephedrine (20 g, 121 mmol) and 150 mL of toluene, and the resulting solution was transferred *via* cannula to the first Schlenk flask. The reaction was allowed to reach R.T. overnight and the mixture was then filtered to remove the morpholine hydrochloride salt and washed with 50 mL of dry toluene. Celite was not used for the filtration;²² instead a porous filter with an extra filter paper was utilized. The yellowish solution was then evaporated under vacuum and the resulting oil solidified upon overnight cooling in the freezer (-30°C). The desired product was recovered as a yellowish waxy solid in 93% yield (25.60 g, 111.48 mmol). No further purification of the product was necessary before being used for the next step.

^1H NMR (CDCl_3 , 400 MHz) δ (ppm): 0.71 (3H, d, $J = 6.5$ Hz, CH_3), 2.69 (3H, d, $J = 5.9$ Hz, NMe), 3.59–3.67 (1H, dq, $J = 6.6$ Hz, CHMe), 5.82 (1H, d, $J = 6.6$ Hz, CHPh), 7.14–7.36 (5H, m, Ar). ^{13}C NMR (CDCl_3 , 100 MHz) δ (ppm): 14.9, 29.5, 88.2, 127.0, 128.7, 136.9. ^{31}P NMR (CDCl_3 , 162 MHz) δ (ppm): 172.4.³¹

(2*R*,4*S*,5*R*)-3,4-Dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]oxazaphospholidine 2-oxide (2) and (2*S*,4*S*,5*R*)-3,4-dimethyl-2-ferrocenyl-5-phenyl-[1,3,2]oxazaphospholidine 2-oxide (3). A Schlenk flask (250 mL) was charged with ferrocene (13.5 g, 72.6 mmol) and $t\text{-BuOK}$ (1.3 g, 11.6 mmol). Dry THF (150 mL) was added, the mixture was cooled to -78°C with a bath of dry ice and acetone, and then $t\text{-BuLi}$ (47.0 mL, 79.8 mmol) was carefully added. The reaction was stirred for around 10 min before being allowed to reach R.T. After 1 hour stirring a fine red-brick precipitate was formed. The slurry was cooled back to -78°C and then carefully divided *via* syringe into two other Schlenk flasks (250 mL) each containing a solution of **1** (12.50 g, 54.4 mmol) in dry THF (75 mL). One of them (A) was previously cooled with an ice bath for 30 min and then 2.5 h with a dry ice–acetone bath (-78°C). The other reaction (B) had been at R.T. for 3 h. Reaction mixture A was allowed to slowly reach

R.T. After overnight stirring, both mixtures were cooled to 0 °C with an ice bath and ^tBuOOH (10 mL, 55 mmol) was added to each of the reactions. After 1 h the baths were removed and the mixtures stirred at R.T. for 3 h; then the mixtures were washed with a saturated solution of Na₂S₂O₃, extracted with EtOAc and dried over MgSO₄. Following evaporation the crude mixtures were purified by flash chromatography on silica gel using EtOAc as eluent. Upon purification the products were crystallized by being dissolved in warm EtOAc, slowly crystallizing into brown crystals on cooling to be analyzed by X-ray diffraction. In both reactions, **2** and **3** were afforded but in different ratios. Reaction using solution A: **2** (6.70 g, 16.95 mmol, 46.5%); **3** (2.63 g, 6.65 mmol, 18.3%). Reaction B: **2** (3.59 g, 9.08 mmol, 24.9% yield); **3** (5.32 g, 13.46 mmol, 36.9%).

2: Mp: 160–162 °C. ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 0.82 (3H, d, *J* = 6.4 Hz, CH₃), 2.56 (3H, d, *J* = 10.2 Hz, NMe), 3.59 (1H, ddq, *J* = 6.4 Hz, *J'* = 10.8 Hz, CHMe), 4.34 (5H, s, Cp), 4.35 (1H, m, subst. Cp), 4.43 (2H, m, subst. Cp), 4.70 (1H, m, subst. Cp), 5.47 (1H, t (dd), *J* = 6.7 Hz, CHPh), 7.31–7.50 (5H, m, Ph). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 15.0, 29.2, 59.2, 70.3, 71.6, 71.7, 74.2, 82.6, 127.1, 128.6, 128.8, 137.0. ³¹P NMR (CDCl₃, 162 MHz) δ (ppm): 40.8. [α]_D²⁰ = 140° (*c* = 1 CHCl₃). HRMS calcd for C₂₀H₂₂FeNO₂P, [M + Na]⁺: 418.0635. Found: 418.0644. Anal. calcd for C₂₀H₂₂FeNO₂P: C (60.78%), H (5.61%), N (3.54%); found: C (60.62%), H (5.66%), N (3.49%).²²

3: Mp: 175–176 °C. ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 0.72 (3H, d, *J* = 6.6 Hz, CH₃), 2.70 (3H, d, *J* = 9.1 Hz, NMe), 3.74 (1H, dq, *J* = 6.2 Hz, *J'* = 6.6 Hz, CHMe), 4.40 (5H, s, Cp), 4.41 (1H, m, subst. Cp), 4.46 (2H, m, subst. Cp), 4.73 (1H, m, subst. Cp), 5.88 (1H, d, *J* = 6.1 Hz, CHPh), 7.32–7.44 (5H, m, Ph). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 14.3, 29.7, 61.3, 66.4, 70.5, 71.8, 72.0, 72.3, 72.4, 74.7, 74.9, 80.3, 126.0, 128.4, 128.9, 137.1. ³¹P NMR (CDCl₃, 162 MHz) δ (ppm): 37.9. [α]_D²⁰ = –320° (*c* = 1.0 CHCl₃). HRMS calcd for C₂₀H₂₂FeNO₂P, [M + H]⁺: 396.0816; found: 396.0813. [M + Na]⁺: 418.0635; found: 418.0606. Anal. calcd for C₂₀H₂₂FeNO₂P: C (60.78%), H (5.61%), N (3.54%); found: C (61.06%), H (5.76%), N (3.95%).

Typical procedure for the *ortho*-lithiation reactions

(**2S,4S,5R**)-3,4-Dimethyl-2-(*α*-(*S_p*)-diphenyl-phosphanyl-ferrocenyl)-5-phenyl-[1,3,2]oxazaphospholidine 2-oxide (**4**). A Schlenk tube was charged with **3** (1.00 g, 2.53 mmol) and dry THF was added. The solution was cooled to –78 °C for 30 min before ^tBuLi (1.7 M) (2.4 mL, 4.0 mmol, 1.6 eq.) was added. The reaction was stirred at –78 °C for another hour before chlorodiphenylphosphine (0.7 mL, 3.9 mmol, 1.5 eq.) was added. After overnight stirring at R.T., analysis of the reaction mixture by TLC (EtOAc) revealed the presence of a new compound. The crude product was analyzed by ¹H and ³¹P NMR, extracted with EtOAc (3 × 75 mL), washed with brine and dried over MgSO₄. Evaporation of the solvent under reduced pressure and purification by flash chromatography using EtOAc as eluent on silica gel afforded the pure product as an orange solid in 60.7% yield (0.89 g, 1.54 mmol). The product was crystallized by being dissolved in warm EtOAc, slowly crystallizing into brown crystals on cooling which were analysed by X-ray diffraction.

Mp: 190–191 °C. ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 0.63 (3H, d, *J* = 6.6 Hz, CH₃), 2.04 (3H, d, *J* = 9.3 Hz, NMe), 3.55 (1H, dq, *J* = 6.2 Hz, *J'* = 6.3 Hz, CHMe), 3.90 (1H, s, subst. Cp), 4.38 (5H, s, Cp), 4.51 (1H, m, subst. Cp), 4.66 (1H, m, subst. Cp), 5.82 (1H, d, *J* = 5.9 Hz, CHPh), 7.24–7.57 (15H, m, Ph). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 14.5, 29.5, 61.9, 71.6, 72.8, 75.2, 75.9, 79.9, 125.9, 128.5, 128.6, 129.2, 133.9, 134.1, 135.0, 135.2, 137.2, 137.3, 138.6, 138.8, 140.7, 140.8. ³¹P NMR (CDCl₃, 162 MHz) δ (ppm): –19.8, 35.9. [α]_D²⁰ = –80° (*c* = 1.0 CHCl₃). HRMS calcd for C₃₂H₃₁FeNO₂P₂, [M + H]⁺: 580.1258; found: 580.1252. Anal. calcd for C₃₂H₃₁FeNO₂P₂: C (66.34%), H (5.27%), N (2.31%); found: C (66.16%), H (5.46%), N (2.38%).

(**2S,4S,5R**)-3,4-Dimethyl-2-(*α*-(*S_p*)-dicyclohexyl-phosphanyl-ferrocenyl)-5-phenyl-[1,3,2]oxazaphospholidine 2-oxide (**5**). Compound **3** (0.87 g, 2.20 mmol), ^tBuLi (1.7 M) (1.9 mL, 3.3 mmol, 1.5 eq.) and chloro-dicyclohexylphosphine (0.5 mL, 2.26 mmol, 1.0 eq.) were used in this reaction. Following the same procedure as for **4**, the compound was purified by flash chromatography using EtOAc as eluent and the pure product was recovered as an orange solid in 49.2% yield (0.64 g, 1.08 mmol).

Mp: 77–78 °C. ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 0.73 (3H, d, *J* = 6.6 Hz, CH₃), 1.13–2.41 (22H, m, Cy), 2.78 (3H, d, *J* = 9.3 Hz, NMe), 3.64–3.76 (1H, dq, *J* = 6.4 Hz, *J'* = 5.9 Hz, CHMe), 4.40 (6H, s, Cp), 4.55 (2H, m, subst. Cp), 5.88 (1H, d, *J* = 5.9 Hz, CHPh), 7.26–7.45 (5H, m, Ph). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 14.7, 26.9, 27.9, 62.1, 71.6, 73.2, 79.8, 126.0, 128.3, 128.9. ³¹P NMR (CDCl₃, 162 MHz) δ (ppm): –9.2, 37.4. [α]_D²⁰ = –80° (*c* = 1.0 CHCl₃). HRMS calcd for C₃₂H₄₃FeNO₂P₂, [M + H]⁺: 592.2197; found 592.2213. Anal. calcd for C₃₂H₄₃FeNO₂P₂: C (64.98%), H (7.33%), N (2.37%); found: C (64.63%), H (7.42%), N (2.28%).

(**2S,4S,5R**)-3,4-Dimethyl-2-(*α*-(*S_p*)-methyl-ferrocenyl)-5-phenyl-[1,3,2]oxazaphospholidine 2-oxide (**6**). Compound **3** (2.50 g, 6.33 mmol), ^tBuLi (1.7 M) (6.3 mL, 9.5 mmol, 1.5 eq.) and iodomethane (0.8 mL, 12.65 mmol, 2.0 eq.) were used in this reaction. Following the same procedure as for **4**, the compound was purified by flash chromatography using EtOAc–hexane (3 : 1) and the pure product was recovered as an orange oil in 46.4% yield (1.19 g, 2.93 mmol). ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 0.58 (3H, d, *J* = 6.4 Hz, CH₃), 2.22 (3H, s, CH₃), 2.56 (3H, d, *J* = 9.3 Hz, NMe); 3.57–3.66 (1H, dq, *J* = 6.4 Hz, *J'* = 6.3 Hz, CHMe), 4.19 (2H, m, subst. Cp), 4.23 (5H, s, Cp), 4.26 (1H, m, subst. Cp), 5.79 (1H, d, *J* = 5.9 Hz, CHPh), 7.20–7.40 (5H, m, Ph). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 12.5, 13.4, 28.0, 59.9, 64.3, 66.2, 68.7, 69.4, 69.5, 72.4, 78.9, 89.4, 124.5, 126.8, 127.5, 135.8. ³¹P NMR (CDCl₃, 162 MHz) δ (ppm): 37.7. [α]_D²⁰ = –320° (*c* = 1.0 CHCl₃). HRMS calcd for C₂₁H₂₄FeNO₂P, [M + Na]⁺: 432.0792; found: 432.0788. Anal. calcd for C₂₁H₂₄FeNO₂P: C (61.63%), H (5.91%), N (3.42%); found: C (61.18%), H (6.12%), N (3.20%).

(**2S,4S,5R**)-3,4-Dimethyl-2-(*α*-(*S_p*)-trimethylsilylferrocenyl)-5-phenyl-[1,3,2]oxazaphospholidine 2-oxide (**7**). Compound **3** (2.00 g, 5.06 mmol), ^tBuLi (1.7 M) (4.5 mL, 7.6 mmol, 1.5 eq.) and chloro-trimethylsilane (1.3 mL, 10.00 mmol, 2.0 eq.) were

used in this reaction. Following the same procedure as for **4**, the compound was purified by flash chromatography using EtOAc–hexane (3 : 1) and the pure product was recovered as an orange solid in 46.5% yield (1.10 g, 2.35 mmol). The product was crystallized by being dissolved in warm EtOAc, slowly crystallizing into brown crystals on cooling which were analysed by X-ray diffraction.

Mp: 118–119 °C. ^1H NMR (CDCl_3 , 400 MHz) δ (ppm): 0.41 (9H, s, TMS), 0.76 (3H, d, $J = 6.7$ Hz, CH_3), 2.63 (3H, d, $J = 9.3$ Hz, NMe), 3.67–3.76 (1H, dq, $J = 6.6$ Hz, $J' = 6.5$ Hz, CHMe), 4.38 (5H, s, Cp), 4.44 (1H, m, subst. Cp), 4.53 (1H, m, subst. Cp), 4.58 (1H, m, subst. Cp), 5.87 (1H, d, $J = 5.9$ Hz, CHPh), 7.33–7.54 (5H, m, Ph). ^{13}C NMR (CDCl_3 , 100 MHz) δ (ppm): 0.0, 13.2, 28.3, 60.2, 68.9, 72.4, 72.6, 73.5, 73.7, 88.7, 124.6, 126.9, 127.5, 135.8, 135.9. ^{31}P NMR (CDCl_3 , 162 MHz) δ (ppm): 38.8. $[\alpha]_{\text{D}}^{20} = 400^\circ$ ($c = 1.0$ CHCl_3). HRMS calcd for $\text{C}_{23}\text{H}_{30}\text{FeNO}_2\text{PSi}$, $[\text{M} + \text{H}]^+$: 468.1211; found: 468.1209. $[\text{M} + \text{Na}]^+$: 490.1031; found: 490.1036. Anal. calcd for $\text{C}_{23}\text{H}_{30}\text{FeNO}_2\text{PSi}$: C (59.10%), H (6.47%), N (3.00%); found: C (59.30%), H (6.65%), N (2.73%).

(2S,4S,5R)-3,4-Dimethyl-2-(α -(S_p)-triethylsilylferrocenyl)-5-phenyl-[1,3,2]oxazaphospholidine 2-oxide (8). Compound **3** (2.10 g, 5.31 mmol), $^t\text{BuLi}$ (1.7 M) (4.4 mL, 7.4 mmol, 1.4 eq.) and chloro-triethylsilane (1.3 mL, 7.7 mmol, 1.45 eq.) were used in this reaction. Following the same procedure as for **4**, the compound was purified by flash chromatography using EtOAc–hexane (3 : 1) and the pure product was recovered as an orange solid in 47.0% yield (1.27 g, 2.50 mmol).

Mp: 68–69 °C. ^1H NMR (CDCl_3 , 400 MHz) δ (ppm): 0.68 (3H, d, $J = 6.6$ Hz, CH_3), 0.78–1.1 (15H, m, TES), 2.53 (3H, d, $J = 9.3$ Hz, NMe), 3.58–3.68 (1H, dq, $J = 6.6$ Hz, $J' = 6.5$ Hz, CHMe), 4.30 (5H, s, Cp), 4.35 (1H, m, subst. Cp), 4.45 (1H, m, subst. Cp), 4.54 (1H, m, subst. Cp), 5.79 (1H, d, $J = 6.2$ Hz, CHPh), 7.25–7.38 (5H, m, Ph). ^{13}C NMR (CDCl_3 , 100 MHz) δ (ppm): 4.0, 7.1, 13.4, 28.2, 60.2, 69.0, 72.7, 72.8, 73.4, 73.6, 78.2, 78.3, 78.5, 124.6, 126.9, 127.5, 135.8, 135.9. ^{31}P NMR (CDCl_3 , 162 MHz) δ (ppm): 40.6. $[\alpha]_{\text{D}}^{20} = -380^\circ$ ($c = 1.0$ CHCl_3). HRMS calcd for $\text{C}_{26}\text{H}_{36}\text{FeNO}_2\text{PSi}$, $[\text{M} + \text{Na}]^+$: 532.1500; found: 532.1476. Anal. calcd for $\text{C}_{26}\text{H}_{36}\text{FeNO}_2\text{PSi}$: C (61.29%), H (7.12%), N (2.75%). Found: C (61.01%), H (7.22%), N (2.59%).

(2S,2S',4S,4'S,5R,5'R)-2-((S_p) ,2'-(S_p)-(phenylphosphinediyl)bis(ferrocen-2,1-diyl))bis(3,4-dimethyl-5-phenyl-[1,3,2]oxazaphospholidine 2-oxide (9). Compound **3** (2.00 g, 5.06 mmol, 2.1 eq.), $^t\text{BuLi}$ (1.7 M) (3.9 mL, 6.6 mmol, 1.3 eq.) and dichlorophenylphosphine (0.33 mL, 2.45 mmol) were used in this reaction. Following the same procedure as for **4**, the compound was purified by flash chromatography using EtOAc as eluent and the pure product was recovered as an orange solid in 56.7% yield (1.24 g, 1.39 mmol).

Mp: 145–146 °C. ^1H NMR (CDCl_3 , 400 MHz) δ (ppm): 0.51 (3H, d, $J = 6.6$ Hz, CH_3), 0.82 (3H, d, $J = 6.6$ Hz, CH_3), 1.89 (3H, d, $J = 9.3$ Hz, NMe), 3.07 (3H, d, $J = 9.9$ Hz, NMe), 3.49 (1H, dq, $J = 6.5$, $J' = 6.3$, CHMe), 3.75 (1H, dq, $J = 6.3$, $J' = 5.7$, CHMe), 3.95 (5H, s, Cp), 4.35 (5H, s, Cp), 4.49–4.78 (6H, m, subst. Cp), 5.75 (1H, d, $J = 5.7$ Hz, CHPh), 5.89 (1H, d, $J = 5.7$ Hz, CHPh); 7.27–7.40 (15H, m, Ph). ^{13}C NMR (CDCl_3 ,

100 MHz) δ (ppm): 14.3, 15.3, 29.5, 62.1, 71.6, 79.9, 80.4, 125.9, 126.5, 128.1, 128.2, 128.3, 128.8, 128.9, 135.1, 135.3, 137.2. ^{31}P NMR (CDCl_3 , 162 MHz) δ (ppm): –37.2, 35.9, 38.8. $[\alpha]_{\text{D}}^{20} = -40^\circ$ ($c = 1.0$ CHCl_3). HRMS calcd for $\text{C}_{46}\text{H}_{47}\text{Fe}_2\text{N}_2\text{O}_4\text{P}_3$, $[\text{M} + \text{Na}]^+$: 919.1345. Found: 919.1305.

(2R,2R',4S,4'S,5R,5'R)-2-((R_p) ,2'-(R_p)-(phenylphosphinediyl)-bis(ferrocen-2,1-diyl))bis(3,4-dimethyl-5-phenyl-[1,3,2]oxazaphospholidine 2-oxide (10). Compound **2** (2.00 g, 5.06 mmol, 2.0 eq.), $^t\text{BuLi}$ (1.7 M) (4.0 mL, 6.8 mmol, 1.35 eq.) and dichlorophenylphosphine (0.3 mL, 2.5 mmol) were used in this reaction. Following the same procedure as for **4**, the compound was purified by flash chromatography using EtOAc as eluent and the pure product was recovered as an orange solid in 66.1% yield (1.55 g, 1.73 mmol).

Mp: 146–147 °C. ^1H NMR (CDCl_3 , 400 MHz) δ (ppm): 0.68 (3H, d, $J = 6.6$ Hz, CH_3), 0.98 (3H, d, $J = 6.6$ Hz, CH_3), 2.23 (3H, d, $J = 10.4$ Hz, NMe), 3.07 (3H, d, $J = 11.2$ Hz, NMe), 3.35 (1H, ddq, $J = 6.4$, $J' = 6.6$, CHMe), 3.87 (5H, s, Cp), 4.18 (5H, s, Cp), 4.24 (1H, ddq, $J = 6.6$ Hz, $J' = 6.4$ Hz, CHMe), 4.57–4.70 (6H, m, subst. Cp), 4.92 (1H, m, CHPh), 6.30 (1H, m, CHPh), 7.26–7.37 (10H, m, Ph), 7.67–7.78 (5H, m, Ph). ^{13}C NMR (CDCl_3 , 100 MHz) δ (ppm): 16.0, 29.1, 30.0, 59.0, 59.3, 60.7, 71.4, 72.6, 73.4, 81.5, 127.0, 127.1, 128.0, 128.3, 128.6, 129.3, 134.4, 134.7, 137.4, 137.9, 142.7. ^{31}P NMR (CDCl_3 , 162 MHz) δ (ppm): –38.4, 38.3, 39.8. $[\alpha]_{\text{D}}^{20} = -240^\circ$ ($c = 1.0$ CHCl_3). HRMS calcd for $\text{C}_{46}\text{H}_{47}\text{Fe}_2\text{N}_2\text{O}_4\text{P}_3$, $[\text{M} + \text{Na}]^+$: 919.1345; found: 919.1310. Anal. calcd for $\text{C}_{46}\text{H}_{47}\text{Fe}_2\text{N}_2\text{O}_4\text{P}_3$: C (61.63%), H (5.28%), N (3.12%); found: C (61.48%), H (5.34%), N (3.08%).

(2S,4S,5S)-3,4-Dimethyl-2-(α -(S_p)-trimethylsilyl-ferrocenyl)-5-phenyl-5-diphenyl-phosphanyl-[1,3,2]oxazaphospholidine 2-oxide (12). A Schlenk tube was charged with compound **7** (0.805 g, 1.72 mmol) and dry THF was added. The mixture was cooled to –78 °C for 30 min before $^t\text{BuLi}$ (1.5 mL, 2.58 mmol, 1.5 eq.) was added. The reaction was stirred at –78 °C for another hour before chlorodiphenylphosphine (0.6 mL, 3.4 mmol, 2.0 eq.) was added. After overnight stirring at room temperature, analysis of the reaction mixture by TLC (EtOAc–hexane 1 : 1) revealed the presence of a new compound. The crude product was analyzed with ^1H and ^{31}P NMR, extracted with EtOAc (2 \times 50 mL), washed with brine and dried over MgSO_4 . Evaporation of the solvent and purification by flash chromatography using EtOAc–hexane (1 : 1) as eluent on silica gel afforded the pure product as an orange oil in 90% yield (1.01 g, 1.55 mmol).

^1H NMR (CDCl_3 , 400 MHz) δ (ppm): 0.32 (9H, s, TMS), 1.75 (3H, d, $J = 7.2$ Hz, CH_3), 2.65 (3H, d, $J = 9.7$ Hz, NMe), 4.28 (5H, s, Cp), 4.40 (1H, s, subst. Cp), 4.56 (1H, s, subst. Cp), 4.89 (1H, s, subst. Cp), 6.05 (1H, dd, $J = 6.6$ Hz, $J' = 7.0$ Hz, CHMe), 7.13–7.60 (15H, m, Ph). ^{13}C NMR (CDCl_3 , 100 MHz) δ (ppm): 12.3, 27.6, 31.0, 68.9, 71.6, 71.7, 74.6, 77.2, 108.6, 126.9, 127.4, 127.5, 128.0, 131.1, 131.3, 131.8, 132.0. ^{31}P NMR (CDCl_3 , 162 MHz) δ (ppm): 29.4 (P(O)Eph, $J_{\text{PP}} = 76.3$ Hz), 46.4 (PPh₂, $J_{\text{PP}} = 75.3$ Hz). $[\alpha]_{\text{D}}^{20} = -100^\circ$ ($c = 1.0$ CHCl_3). HRMS calcd for $\text{C}_{35}\text{H}_{39}\text{FeNO}_2\text{P}_2\text{Si}$, $[\text{M} + \text{H}]^+$: 652.1653; found: 652.1627. Anal. calcd for $\text{C}_{35}\text{H}_{39}\text{FeNO}_2\text{P}_2\text{Si}$: C

(64.52%), H (6.03%), N (2.15%); found: C (64.68%), H (6.08%), N (2.20%).

(2*S*,4*S*,5*S*)-3,4-Dimethyl-2-(α -(*S_p*)-methyl-ferrocenyl)-5-phenyl-5-diphenyl-phosphanyl-[1,3,2]oxazaphospholidine 2-oxide (13). Compound **6** (0.74 g, 1.81 mmol), ^tBuLi (1.7 M) (1.6 mL, 2.7 mmol, 1.5 eq.) and chlorodiphenylphosphine (0.6 mL, 3.1 mmol, 1.7 eq.) were used in this reaction. Following the same procedure as for **12**, the compound was purified by flash chromatography using EtOAc–hexane (1 : 1) and the pure product was recovered as an orange oil in 85.7% yield (0.92 g, 1.55 mmol).

¹H NMR (CDCl₃, 400 MHz) δ (ppm): 1.65 (3H, d (dd), *J* = 7.2 Hz, *J*_{PH} = 1.3 Hz, CH₃), 1.98 (3H, s, CH₃), 2.45 (3H, d (dd), *J* = 10.2 Hz, *J*' = 2.3 Hz, NMe), 4.13 (1H, s, subst. Cp), 4.14 (5H, s, Cp), 4.18 (1H, s, subst. Cp), 4.38 (1H, s, subst. Cp), 5.88–5.95 (1H, dq, *J* = 7.2 Hz, *J*' = 6.7 Hz, *J*_{PH} = 2.3 Hz CHMe), 7.09–7.40 (15H, m, Ph). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 12.2, 13.0, 30.7, 69.5, 71.9, 72.0, 86.3, 86.4, 109.5, 109.6, 126.9, 127.0, 127.1, 128.0, 130.1, 131.0, 132.0, 132.2, 133.7, 134.0, 135.1, 135.3, 145.1, 145.2. ³¹P NMR (CDCl₃, 162 MHz) δ (ppm): 30.0 (P(O)Eph, *J*_{PP} = 81.3 Hz), 48.4 (PPh₂, *J*_{PP} = 83.2 Hz). [α]_D²⁰ = –60° (*c* = 1.0 CHCl₃). HRMS calcd for C₃₃H₃₃FeNO₂P₂, [M + H]⁺: 594.1414; found: 594.1440. [M + Na]⁺: 616.1234, found: 616.1204. Anal. calcd for C₃₃H₃₃FeNO₂P₂: C (66.79%), H (5.61%), N (2.36%); found: C (66.73%), H (5.64%), N (2.31%).

(2*S*,4*S*,5*S*)-3,4-Dimethyl-2-(α -(*S_p)-diphenyl-phosphanyl-ferrocenyl)-5-phenyl-5-diphenyl-phosphanyl-[1,3,2]oxazaphospholidine 2-oxide (14).* Compound **4** (0.74 g, 1.81 mmol), ^tBuLi (1.7 M) (1.6 mL, 2.7 mmol, 1.5 eq.) and chlorodiphenylphosphine (0.6 mL, 3.1 mmol, 1.7 eq.) were used in this reaction. Following the same procedure as for **12**, the compound was purified by flash chromatography using EtOAc–hexane (1 : 1) and the pure product was recovered as an orange solid in 53.1% yield (0.92 g, 1.55 mmol). Mp: 58–60 °C.

¹H NMR (CDCl₃, 400 MHz) δ (ppm): 1.58 (3H, d, *J* = 7.2 Hz, CH₃), 2.04 (3H, d, *J* = 10.1 Hz, NMe), 3.89 (1H, s, subst. Cp), 4.06 (5H, s, Cp), 4.40 (1H, d, *J* = 2.3 Hz subst. Cp), 4.89 (1H, s, subst. Cp), 5.97–6.03 (1H, dq, *J* = 7.2 Hz, *J*' = 7.4 Hz, *J*_{PH} = 1.9 Hz CHMe), 6.74–7.51 (25H, m, Ph). ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 12.3, 13.0, 30.2, 70.2, 71.1, 80.3, 86.4, 126.5, 126.8, 127.0, 127.4, 127.8, 128.1, 130.2, 131.0, 131.2, 131.7, 131.9, 132.4, 132.6, 133.9, 134.2, 135.1, 135.3, 137.9, 138.1, 139.5, 139.6, 145.3, 145.4. ³¹P NMR (CDCl₃, 162 MHz) δ (ppm): –19.0 (PPh₂ (Cp)), 27.6 (P(O)Eph, *J*_{PP} = 77.3 Hz), 47.3 (PPh₂ (C(PPh₂)Ph), *J*_{PP} = 75.3 Hz). [α]_D²⁰ = +120° (*c* = 1.0 CHCl₃). HRMS calcd for C₄₄H₄₀FeNO₂P₃ [M + Na]⁺: 786.1519; found: 786.1522. Anal. calcd for C₄₄H₄₀FeNO₂P₃: C (69.21%), H (5.28%), N (1.83%); found: C (68.73%), H (5.37%), N (1.59%).

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Notes and references

- 1 For the FDA's policy statement for the development of new stereoisomeric drugs, see: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122883.htm>
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