Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 14, pp. 2337–2346, 1997

Printed in Great Britain
PII: S0957-4166(97)00246-2
0957-4166/97 $17.00 + 0.00

Chiral ferrocenyl-oxazolines incorporating thioether units: effective ligands for palladium-catalysed allylic substitution

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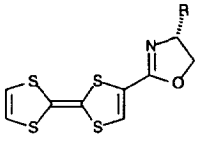
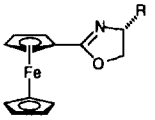
Abstract: The syntheses of novel ferrocene-based chiral oxazolines **17, 18** and **26** are reported. The application of these compounds as catalysts for asymmetric palladium-catalysed allylic substitution reactions has been investigated. These reactions afford the substitution products in both high yield and high enantiomeric excess. The solution electrochemical redox-behaviour of **17, 18** and **26** in the presence of palladium ions establishes that palladium coordination to the oxazoline results in a significant anodic shift in the redox potential of the ferrocene ligand. The X-ray crystal structure of the ferrocene-hydroxy amide derivative **16** is also reported. © 1997 Elsevier Science Ltd

Introduction

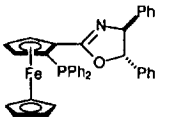
The use of chiral modifiers to control the enantioselectivity of a variety of organic transformations in which two product enantiomers are possible, is a burgeoning topic,[1] particularly when the modifier can be employed in a catalytic fashion.[2] Our interest in developing systems in which an electrochemical response is observed in a ligand when a metal was complexed,[3] led us to postulate[4] that a chiral ligand appended to a redox active unit should be capable of performing a chiral transformation with the subsequent decomplexation of the metallic-intermediate upon electrochemical oxidation, thus facilitating a catalytic cycle. We recently studied chiral oxazolines appended to tetrathiafulvalene (TTF) **1** as a means of providing a chiral environment intimately attached to a redox-active unit.[4] Oxazolines have several advantages as sources of chirality, the principal being that they are readily accessible from homochiral amino alcohols and have proved to be effective catalysts in a variety of reactions.[5] Recently, ferrocenyl-oxazolines **2** have been independently synthesised by several groups;[6] the directed *ortho*-lithiation of the ferrocene ring has been studied[6a–d] and a subsequent derivative **3** has been employed in the hydrosilylation of ketones in the presence of iridium.[6f]



1 R = ^{i}Pr, ^{t}Bu, Ph



2 a R = H
b R = ^{i}Pr



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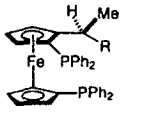
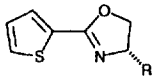
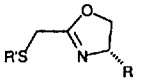


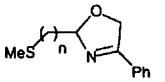
4 R = OH, NMe_2



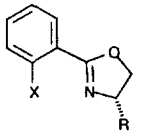
5 R = alkyl



6 R = alkyl
R'= aryl, alkyl



7 n = 1, 2



8 R = alkyl, X = ArS
9 R = alkyl, X = Ph_2P

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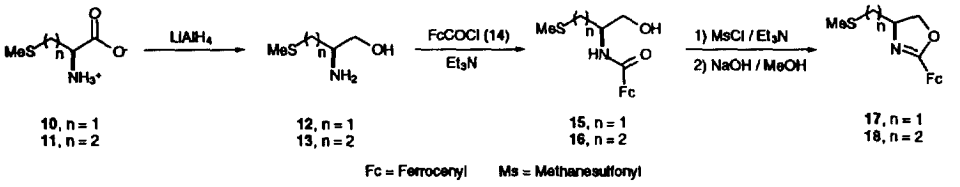
Of particular interest to our research, was the report by Hayashi *et al.* that ferrocene- oxazoline systems, typified by **4**, had been successfully applied to palladium-catalysed allylic substitution reactions.[7] The electrochemical behaviour of systems **4** had, however, been ignored despite the well-documented redox chemistry of ferrocene.[8] Recently, oxazoline catalysts **5–9** incorporating either phosphorus or sulfur atoms as auxiliary binding sites have been successfully applied to both palladium-catalysed allylic substitutions and metal-catalysed hydrosilylation reactions.[9] However, none of these systems contain the redox-active ferrocene moiety which we believed would be important in providing an effective catalyst which could show high activity coupled with redox-addressibility.

Results and discussion

Several workers[9a–e] have reported the use of a second heteroatom binding site to induce an electronic bias in the allyl–palladium intermediates we proposed to study. In the case of our previous catalysts **1**, this was a sulfur atom of the TTF unit attached to the 2-position of the oxazoline. For our target ferrocene catalysts, it was decided to incorporate the donor atom in the 4-position of the oxazoline rather than directly on the ferrocene ring itself, since suitable homochiral amino alcohols are readily accessible.

The synthesis of oxazolines **17** and **18** is detailed in Scheme 1. Reduction of both *S*-methyl-L-cysteine **10** and methionine **11** with lithium aluminium hydride readily afforded the corresponding amino alcohols **12**, and **13** containing a thioether linkage.[9d,10] Treatment of the amino alcohols with freshly prepared ferrocene-carbonyl chloride **14**[11] cleanly gave the ferrocene-hydroxy amides **15**, **16** in excellent yields. Initial attempts to cyclise these compounds to the corresponding oxazolines under Appel conditions (PPh_3, Et_3N, CCl_4)[12] proved disappointing, yielding products heavily contaminated with triphenylphosphine oxide, which could not be easily removed. An alternative route, involving mesylation of the free hydroxyl group of **15** and **16** and subsequent cyclisation with sodium hydroxide in methanol[13] was, however, extremely clean, giving oxazolines **17** and **18** in 70% and 72% yields, respectively.



Scheme 1.

An X-ray crystallographic study of **16** proved the expected stereochemistry. The *S* configuration of the asymmetric centre C(12) (see Figure 1), determined from anomalous X-ray scattering, corresponds to the L-configuration of the initial cysteine.

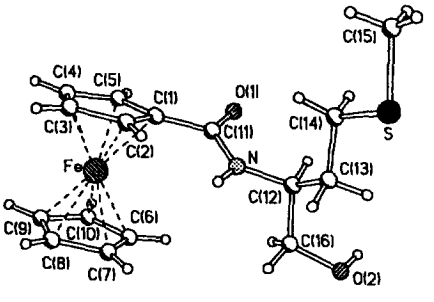
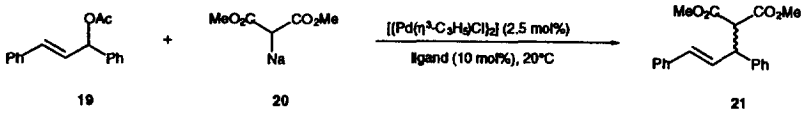


Figure 1. X-ray molecular structure of **16**.

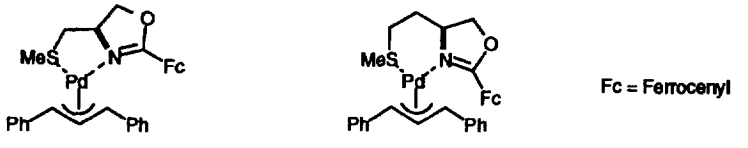
With systems **17** and **18** in hand, their application in palladium-catalysed allylic substitution reactions was investigated. Allylic acetate **19**[14] reacted with the sodium salt of dimethyl malonate **20** in the presence of allylpalladium chloride dimer (2.5 mol%) and either **17** or **18** (10 mol%) in the solvent stated, to afford the substitution product **21** (Scheme 2) as shown in Table 1.



19 **20** **21**

Scheme 2.

Table 1 shows that both **17** and **18** successfully catalysed the substitution reaction in a variety of solvents. It can readily be seen that **18** is more effective than **17** in transferring chirality in this reaction (compare entries 1 and 2). This is presumably due to the increased tether length between the donor atoms which coordinate palladium in **18**, bringing the asymmetric environment closer to the allyl species during the reaction, as can be seen by consideration of transition states **22** and **23**.[15]



22 **23**

Indeed, both catalysts **17** and **18** afford **21** in reasonable enantiomeric excess even in highly polar solvents such as DMF (entries 3, 4 and 7). This is interesting given the fact that previous ligands, typified by **5–8**, have been shown to give poor enantio-control in DMF due to ligand displacement by the solvent.[9d] The use of more concentrated solutions of **19** led to an increase in the enantioselectivity (*cf.* entries 1 and 4 with 6 and 7). The use of a relatively non-polar solvent (entry 5) afforded the substitution product **21** in high enantiomeric excess but in low yield, which was presumably due to the extreme insolubility of the nucleophile **20** in the reaction solvent, which effectively rendered the whole reaction process heterogeneous.

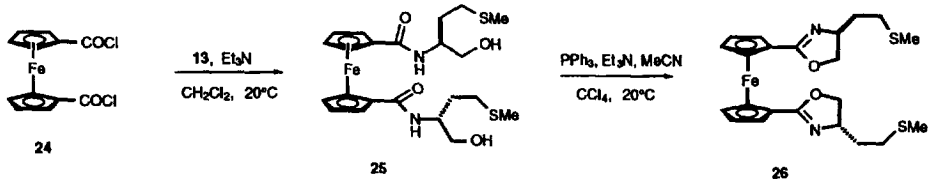
Table 1. Enantioselectivity in palladium allylic substitution reactions using oxazolines **17** and **18**

Entry	Solvent [a]	Ligand	Time (h)	Yield (%) [b]	ee[c] of (+) **21** (%) [d]
1	THF	**17**	48	58	54
2	THF	**18**	48	50	84
3 [e]	DMF	**17**	36	52	60
4	DMF	**18**	36	84	64
5	Toluene	**18**	72	34	87
6 [f]	THF	**18**	36	68	91
7 [f]	DMF	**18**	24	76	79

a) All reactions 0.4 mM in acetate **19** unless stated otherwise. b) Yield of analytically pure product after column chromatography. c) Determined by ^{1}H-NMR in the presence of Pr(hfc)3. d) Determined by optical rotation measurements compared to the value reported by Pfaltz.[16] e) Ligand : Pd ratio 1:4. f) 0.8 mM in **19**.

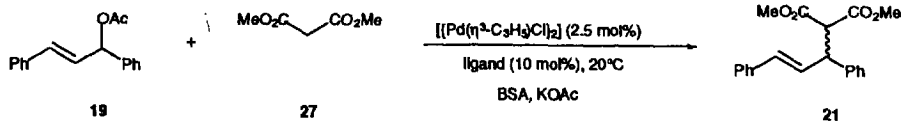
Based on these initial results concerning the rate and yield of the substitution reaction of **19** in polar solvents, and the observation that a ratio of ligand: Pd of 2:1 appeared an effective test scenario, two new approaches were considered: i) the use of a more soluble nucleophile to increase the reaction yield and ii) the synthesis of C_2-symmetrical bis-oxazolines based on the ferrocene core, which would provide two identical catalytic sites per molecule of ligand.[17]

The route to the C_2-symmetrical system **26** (Scheme 3) began with ferrocene-1,1′-dicarbonyl chloride **24**,[18] which was reacted with β-hydroxy amine **13** to afford bis-amide **25**. Attempts to cyclise **25** *via* the bis mesylate using triethylamine[6b] or methanolic sodium hydroxide[13] both afforded product **26** in very poor yields. The use of Appel conditions[12] did, however, provide the requisite homochiral bis-oxazoline **26** in reasonable yield.



Scheme 3.

In order to overcome the problems of solubility encountered when **20** was employed as the nucleophile, the modification employed by Williams[9d] utilising *N,O*-bis-trimethylsilyl acetimide (BSA) was investigated. Thus, acetate **19** was treated with BSA, potassium acetate and dimethylmalonate **27** in the presence of allylpalladium chloride (2.5 mol%) and either **18** or **26** (10 mol%), in the solvent stated, to afford the substitution product **21** (Scheme 4) as shown in Table 2.



Scheme 4.

As can be seen from Table 2, the use of BSA and dimethylmalonate in the allylic substitution reaction led to greatly improved yields and faster reaction times when compared to the initial route employing **20**. The reactions can be performed in a variety of solvents with dichloromethane providing the highest yield and the highest level of enantioselectivity (entry 2). Interestingly, the use of toluene under the improved conditions (entry 3) afforded **21** in lower enantioselectivity than was observed using the initial route (*cf.* Table 1, entry 5). This may, in part, be due to the insolubility problem previously discussed, in which the concentration of the nucleophile was therefore extremely low, whereas, using the BSA modification, the reaction was homogeneous. The application of bis-oxazoline **26** in a 1:1 ratio with allylpalldium chloride led to lower yields and lower enantioselectivity than was observed for the mono-oxazoline **18** (*cf.* entries 1 and 2 with 5 and 6). These results indicate that the two binding sites in **26** do not function as efficiently as having two equivalents of a catalyst containing a single binding site. The use of a 2:1 ratio of **26**: palladium (entry 7) gave results almost identical to those observed with system **18** (entry 7). The use of an increased amount of potassium acetate (entry 4) led to a depletion of the enantiomeric excess (*cf.* entry 2), which is consistent with previous observations.[9d]

In order to determine whether electrochemical recycling of the new ferrocene systems was feasible, it was first necessary to determine if palladium binding could be detected in the cyclic voltammeric behaviour of **17**, **18** and **26**. We had previously ascertained that TTF oxazolines **1** bound palladium, by conducting titration studies in an electrochemical cell during cyclic voltammetry measurements[4] An identical study was therefore performed. The titration of a standard solution of palladium acetate

Table 2. Enantioselectivity in the formation of **21** using oxazolines **18** and **26** employing BSA in the allylic substitution reaction

Entry	Solvent [a]	Ligand	Time (h)	Yield (%) [b]	ee[c] of (+) **21** (%) [d]
1	THF	**18**	48	98	76
2	CH_2Cl_2	**18**	36	98	93
3	Toluene	**18**	48	93	74
4 [e]	CH_2Cl_2	**18**	36	97	85
5 [f]	THF	**26**	36	70	76
6 [f]	CH_2Cl_2	**26**	24	86	82
7	CH_2Cl_2	**26**	36	93	91

a) All reactions 0.4 mM in acetate **19** unless stated otherwise. b) Yield of analytically pure product after column chromatography. c) Determined by ^{1}H-NMR in the presence of Pr(hfc)$_3$. d) Determined by optical rotation measurements. e) 0.1 equiv. of KOAc added instead of 0.03 equiv. f) Ligand : Pd ratio 1:1.

Table 3. The binding of palladium to ferrocene oxazolines measured by cyclic voltammetry

Oxazoline	$E_1^{1/2}$ / mV	$E_2^{1/2}$ / mV	ΔE / mV	min [Pd] [a]	K_2 / K_1 [b]
2a	+510	+660	150	1	350
17	+520	+620	100	0.5	50
18	+520	+690	170	0.5	750
26	+720	+910	190	1	1500

a) Minimum number of equivalents of palladium required to observe the second redox wave. b) Binding enhancement for the complexation of palladium calculated by a modification of the equation detailed in reference 22.

into a known concentration of either **17, 18** or **26** in dry, degassed acetonitrile showed the appearance of a new, anodically shifted redox peak. The results are summarised in Table 3.

As can be seen from Table 3, in all cases, only equimolar or lower amounts of palladium were required before a second redox peak became clearly observable. Surprisingly, ferrocene-oxazoline **2a** which does not contain a thioether group, still demonstrates an affinity for palladium ions. This may be due to the formation of a three-point complex between the two heteroatoms in the oxazoline ring and the ferrocene iron atom. Stable palladium complexes of ferrocene-1,1′-dithiols have previously been reported[19] and three-point complexes containing an M^+–Fe bond in which the ferrocenyl group acts as a donor in the coordination sphere of the metal are well documented.[20] The binding enhancement K_2/K_1[21] for **2a** is relatively low, which is an indication that palladium is bound weakly to the oxazoline system. Ferrocene-oxazolines **17** and **18**, incorporating the thioether subunit both show palladium binding, that of **17** being less distinct than **2a** whilst **18** showed an improved value for the binding enhancement. It is possible that in both these systems, the presence of the thioether group allows binding to occur as depicted in transition states **22** and **23**. In the latter case, this seems more favourable than a three-point type of arrangement and hence binding is increased; in the former, however, this binding may compete with the three-point mode with the net effect of the two competing binding modes being a reduction in the value of K_2/K_1. Bis-oxazoline **26** also showed the appearance of a

second peak anodically shifted from the original, with a binding enhancement twice that of **18**, a fact presumably due to the two identical binding sites. The fact that the binding is reversible on the cyclic voltammetric timescale indicates that reversible binding of a metallic species may be possible. The binding enhancements observed are also much higher than those seen for systems **1** which could not be measured.[4] This may, in turn, be indicative of a better catalyst binding site.

Conclusions

We have outlined an expedient route to three new homochiral ferrocene-oxazolines **17**, **18** and **26** which incorporate a thioether subunit within their framework. These have been applied to the allylic substitution of acetate **19** *via* two different routes affording the product **21** in good yields and moderate to high enantioselectivities. The binding of palladium to these systems demonstrates that **18** and **26** have a greater affinity for palladium ions than **17** which possesses a shorter tether between the oxazoline ring and the thioether group. The reversibility of this binding is promising in light of the fact that we wish to apply analagous catalysts in reactions where electrochemical recycling is the pivotal step in the catalytic cycle.

Experimental

^{1}H NMR spectra were obtained on a Varian 400 at 399.96 MHz, ^{13}C NMR spectra were obtained on a Varian 400 at 100.58 MHz. Mass spectra were recorded on a VG7070E spectrometer operating at 70 eV. Infra-red spectra were recorded on a Perkin-Elmer 1615 FTIR operated from a Grams Analyst 1600. Optical rotation measurements were performed using an Optical Activity AA-10 polarimeter. Melting points were obtained on a Kofler hot-stage microscope apparatus and are uncorrected. All reagents were of commercial quality and solvents were dried, where necessary, using standard procedures.

Cyclic voltammetric data were measured with iR compensation using a BAS CV50 electrochemical analyser. The experiments were carried with 5 ml of a *ca.* 10^{-4} M solution of compound in acetonitrile containing 0.2 M tetrabutylammonium perchlorate (Fluka, puriss, electrochemical grade) as the supporting electrolyte. The potentials were measured versus platinum wire quasi-reference electrode and corrected versus ferrocene/ferrocinium$^+$ as $E^{1/2}$=+0.36 V by adding ferrocene to the studied solution after the experiment and referenced versus Ag/AgCl

*(4R)-*N*-(1-Hydroxy-3-methylsulfanylmethyl)ferrocenamide* ***15***

To a well-stirred solution of (R)-2-amino-3-(methsulfanyl)propan-1-ol **12** (0.44 g, 3.6 mmol) and anhydrous triethylamine (0.66 g, 6.6 mmol) in anhydrous dichloromethane (30 ml) was added a solution of freshly prepared ferrocene-carbonyl chloride **14** (0.75 g, 3 mmol) in anhydrous dichloromethane (20 ml). The resultant solution was stirred under argon at 20°C overnight before being diluted with dichloromethane (100 ml) and washed with water (2×25 ml). The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo* to afford a dark brown solid. Column chromatography using silica gel (70–230 mesh) and 5% methanol in dichloromethane as the eluting solvent afforded the title compound (0.85 g, 86%) as a yellow solid mp. 118–119°C; δ_H ($CDCl_3$) 2.19 (3H, s), 2.75 (2H, ABX *J*=12, 4.4 Hz), 3.25 (1H, t, *J*=4.4 Hz), 3.85 (2H, m), 4.18 (1H, m), 4.23 (5H, s), 4.38 (2H, t, *J*=1.5 Hz), 4.68 (1H, t, *J*=1.5 Hz), 4.72 (1H, t, *J*=1.5 Hz) and 6.33 (1H, bs); δ_C ($CDCl_3$) 15.5, 35.1, 50.4, 64.9, 68.0, 68.2, 69.8, 70.6, and 150.9; ν_{max} (KBr)/cm^{-1} 1633, 1612, 1541, 1104, and 825; m/z (DCI) 333 (MH^+, 100%); Analysis calculated for $C_{15}H_{19}NFeO_2S$; C 54.07, H 5.75, N 4.20. Observed; C 53.99, H 5.83, N 3.87; $[\alpha]_D^{20}$=−26 (c=0.2, EtOH); $E^{1/2}$+540 mV (reversible).

*(4S)-*N*-(1-Hydroxy-3-ethylsulfanylmethyl)ferrocenamide* ***16***

To a well-stirred solution of (S)-2-amino-4-(methsulfanyl)butan-1-ol **13** (0.49 g, 3.6 mmol) and anhydrous triethylamine (0.66 g, 6.6 mmol) in anhydrous dichloromethane (30 ml) was added a solution of freshly prepared ferrocene-carbonyl chloride **14** (0.75 g, 3 mmol) in anhydrous dichloromethane (20 ml). The resultant solution was stirred under argon at 20°C overnight before being diluted with dichloromethane (100 ml) and washed with water (2×25 ml). The organic phase was dried ($MgSO_4$)

and the solvent removed *in vacuo* to afford a dark brown solid. Column chromatography using silica gel (70–230 mesh) and 5% methanol in dichloromethane as the eluting solvent afforded the title compound (0.79 g, 76%) as an orange solid mp. 108–109°C; δ_H ($CDCl_3$) 1.96 (2H, m), 2.16 (3H, s), 2.64 (2H, t, J=8 Hz), 3.05 (1H, t, J=4 Hz), 3.75 (2H, m), 4.22 (1H, m), 4.23 (5H, s), 4.37 (2H, t, J=1.5 Hz), 4.69 (2H, t, J=1.5 Hz), and 6.24 (1H, d, J=4 Hz); δ_C ($CDCl_3$) 15.7, 30.1, 30.9, 51.6, 65.8, 68.29, 68.2, 69.8, 70.6, 75.5, and 171.5; ν_{max} (KBr)/cm^{-1} 1624, 1543, 1299, and 826; m/z (DCI) 348 (MH^+, 100%); Analysis calculated for $C_{16}H_{21}NFeO_2S$; C 55.37, H 6.10, N 4.03. Observed; C 55.21, H 6.09, N 3.79; $[\alpha]_D^{20}$=+22 (c=0.11, EtOH); $E^{1/2}$+530 mV (reversible).

(4R)-4,5-Dihydro-4-(methylsulfanyl)methyl-2-ferrocenyl-1,3-oxazole ***17***

To an ice-cold solution of amide **15** (0.2 g, 0.6 mmol) in anhydrous dichloromethane (10 ml) was added anhydrous triethylamine (0.14 g, 1.44 mmol) followed by methane sulfonyl chloride (0.09 g, 0.72 mmol). The mixture was stirred at 0°C for 1 h, diluted with dichloromethane (100 ml) and washed with water (2×50 ml). The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo* to afford a red oil which was immediately dissolved in 0.5M NaOH (50 ml, 1:1 water: methanol) and refluxed for 3h. After cooling, the mixture was reduced in volume to *ca.* 20 ml and diluted with water (50 ml), the solution was extracted with dichloromethane (3×25 ml), the organic fractions combined, dried ($MgSO_4$) and the solvent removed *in vacuo* to afford a dark oil. Column chromatography using silica gel (70–230 mesh) and 2% methanol in dichloromethane as the eluting solvent afforded one band. Evaporation of the single yellow band afforded a brown solid which was suspended in warm hexane (50 ml) and filtered. Removal of the hexane *in vacuo* gave the title compound (0.134 g, 70%) as a yellow solid mp. 64–66°C δ_H ($CDCl_3$) 2.10 (3H, s), 2.60 (1H, AB_x J=12, 4.5 Hz), 2.86 (1H, AB_x J=12, 4.5 Hz), 4.19 (1H, m), 4.20 (5H, s), 4.33 (2H, t, J=1.6 Hz), 4.40 (2H, t, J=4.5 Hz), and 4.73 (2H, t, J=1.6 Hz); δ_C ($CDCl_3$) 16.2, 39.1, 66.1, 68.9, 69.0, 69.7, 69.8, 70.3, 70.4, 71.5 and 167.3; ν_{max} (KBr)/cm^{-1} 1645, 1540, and 831; m/z (DCI) 316 (MH^+, 100%); Analysis calculated for $C_{15}H_{17}NFeOS$; C 57.16, H 5.44, N 4.44. Observed; C 57.23, H 5.40, N 4.29; $[\alpha]_D^{20}$=−48 (c=0.22, EtOH); $E^{1/2}$+520 mV (reversible).

(4R)-4,5-Dihydro-4-(methylsulfanyl)ethyl-2-ferrocenyl-1,3-oxazole ***18***

To an ice-cold solution of amide **16** (0.22 g, 0.63 mmol) in anhydrous dichloromethane (10 ml) was added anhydrous triethylamine (0.14 g, 1.44 mmol) followed by methane sulfonyl chloride (0.09 g, 0.72 mmol). The reaction was then carried out in an identical manner to that described for **17**. Column chromatography using silica gel (70–230 mesh) and 1% methanol in dichloromethane as the eluting solvent afforded one band. Evaporation of the yellow band afforded a brown solid which was suspended in warm hexane (100 ml) and filtered. Removal of the hexane *in vacuo* gave the title compound (0.150 g, 72%) as an orange solid mp. 47–49°C δ_H ($CDCl_3$) 1.83–1.97 (2H, m), 2.13 (3H, s), 2.64 (2H, m), 3.98 (1H, t, J=7.9 Hz), 4.19 (5H, s), 4.23 (1H, t, J=8.4 Hz), 4.33 (2H, t, J=1.6 Hz), 4.44 (1H, t, J=8.4 Hz) and 4.74 (2H, t, J=1.6 Hz); δ_C ($CDCl_3$) 15.5, 30.6, 35.4, 65.6, 68.9, 69.05, 69.6, 70.1, 70.3, 70.4, 71.9, and 166.3; ν_{max} (KBr)/cm^{-1} 1650, 1535, and 835; m/z (DCI) 330 (MH^+, 100%); Analysis calculated for $C_{16}H_{19}NFeOS$; C 58.37, H 5.82, N 4.25. Observed; C 58.15, H 5.74, N 3.93; $[\alpha]_D^{20}$−92 (c=0.1, EtOH); $E^{1/2}$+520 mV (reversible).

*1,1′-Bis-(4S)-*N*-(1-hydroxy-3-ethylsulfanylmethyl)ferrocenamide* ***25***

To a well-stirred solution of (S)-2-amino-4-(methsulfanyl)butan-1-ol **13** (0.24 g, 1.75 mmol) and dry triethylamine (0.18 g, 1,75 mmol) in anhydrous dichloromethane (30 ml) was added a solution of freshly prepared ferrocene-1,1′-bis-carbonyl chloride **24** (0.26 g, 0.8 mmol) in anhydrous dichloromethane (20 ml). The resultant solution was stirred under argon at 20°C overnight before being diluted with dichloromethane (100 ml) and washed with water (2×25 ml). The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo* to afford a yellow solid. Column chromatography using silica gel (70–230 mesh) and 5% methanol in dichloromethane as the eluting solvent afforded the title compound (0.37 g, 93%) as an orange solid mp. 40–49°C. δ_H ($CDCl_3$) 1.91 (4H, q, J=7.2

Hz), 2.15 (6H, s), 2.60 (4H, t, *J*=7.2 Hz), 3.69 (2H, d, *J*=5.6 Hz), 3.85 (2H, d, *J*=5.6 Hz), 4.27 (2H, t, *J*=3.2 Hz), 4.32 (2H, t, *J*=2.3 Hz), 4.39 (2H, s), 4.44 (2H, t, *J*=1.6 Hz), 4.50 (2H, t, *J*=1.6 Hz), 4.69 (2H, t, *J*=1.6 Hz) and 6.95 (2H, d, *J*=8.4 Hz); δ_C ($CDCl_3$) 15.5, 30.6, 30.9, 51.1, 64.3, 62.4, 71.5, 77.4 and 170.5; ν_{max} (KBr)/cm^{-1} 3320, 2905, 1680, and 1597; m/z (DCI) 508 (MH^+, 100%); Analysis calculated for $C_{22}H_{32}N_2FeO_4S_2$; C 51.97, H 6.34, N 5.51. Observed; C 51.83, H 6.38, N 5.42; $[\alpha]_D^{20}$=+41.8 (c=0.1, EtOH); $E^{1/2}$+720 mV (reversible).

1,1′-Bis-ferrocene-(4R)-4,5-dihydro-4-(methylsulfanyl)ethyl-1,3-oxazole **26**

To a solution of bis-amide **25** (0.26 g, 0.5 mmol) in anhydrous acetonitrile (25 ml) were added sequentially; anhydrous triethylamine (0.22 g, 2.25 mmol), triphenylphosphine (0.48 g, 1.8 mmol) and anhydrous carbon tetrachloride (1 ml, excess). The resultant mixture was stirred at 20°C under argon for 36 h, whereupon water (50 ml) was added and the mixture extracted with dichloromethane (2×50 ml). The organic portions were combined, dried ($MgSO_4$) and the solvent removed *in vacuo* to afford a brown oil. Column chromatography using silica gel (70–230 mesh) and 2% methanol in dichloromethane as the eluting solvent afforded the title compound (0.135 g, 56%) as a yellow oil. δ ($CDCl_3$) 1.83 (2H, m), 1.96 (2H, m), 2.14 (6H, s), 2.64 (4H, quintet, *J*=4.6 Hz), 3.98 (2H, t, *J*=7.6 Hz), 4.24 (2H, t, *J*=9.2 Hz), 4.35 (4H, t, *J*=1.6 Hz), 4.44 (2H, t, *J*=9.2 Hz) and 4.73 (4H, t, *J*=1.6 Hz); δ_C ($CDCl_3$) 115.5, 30.7, 35.3, 65.7, 70.5, 70.7, 71.8, 72.0, and 165.3; ν_{max} (CH_2Cl_2)/cm^{-1} 2928, 2856, and 1656; m/z (DCI) 473 (MH^+, 100%); HRMS calculated for $C_{22}H_{28}FeN_2O_2S_2$ 472.0975 found 472.0970; $[\alpha]_D^{20}$=−124 (c=0.1, EtOH); $E^{1/2}$+720 mV (quasi-reversible).

Typical procedure for palladium-allylic substitution using sodio-dimethylmalonate as the nucleophile

To [{Pd(η_3-C_3H_5)Cl}$_2$] (4 mg, 0.01 mmol) was added a solution of the ligand (0.04 mmol) in anhydrous solvent (1 ml) and racemic-(*E*)-1,3-diphenylprop-2-enyl acetate **19** (106 mg, 0.4 mmol, 1 equiv.). The solution was stirred at room temperature under argon for 15 min whereupon dimethyl sodiomalonate (64 mg, 0.4 mmol, 1 equiv.) in anhydrous solvent (2 ml) was added. The reaction was stirred for the time noted in Tables 1 and 2 whereupon it was diluted with diethyl ether (50 ml) and washed with saturated ammonium chloride (2×25 ml). The organic phase was separated, dried ($MgSO_4$) and the solvent removed *in vacuo* to afford a colourless oil. Column chromatography on silica gel (70–230 mesh) with hexane/diethyl ether (3:1 v/v) as eluant afforded **21** which was identical to that described in the literature.[15]

Typical procedure for palladium-allylic substitution using BSA

To [{Pd(η_3-C_3H_5)Cl}$_2$] (4 mg, 0.01 mmol) was added a solution of the ligand (0.04 mmol) in anhydrous solvent (1 ml). The resultant solution was stirred for 15 min at room temperature, whereupon, racemic-(*E*)-1,3-diphenylprop-2-enyl acetate **19** (106 mg, 0.4 mmol, 1 equiv.) in anhydrous solvent (1 ml), dimethyl malonate (158 mg, 0.14 ml, 1.2 mmol), *N,O*-bis-trimethylsilyl)acetamide (240 mg, 0.3 ml, 1.2 mmol) and anhydrous potassium acetate (1mg, 0.01 mmol) were added sequentially. The solution was stirred at room temperature under argon for the time noted in Table 2, whereupon it was diluted with diethyl ether (50 ml) and washed with cold saturated ammonium chloride (2×25 ml). The organic phase was separated, dried ($MgSO_4$) and the solvent removed *in vacuo* to afford a colourless oil. Column chromatography on silica gel (70–230 mesh) with hexane/diethyl ether (3:1 v/v) as eluant afforded **21** which was identical to that described in the literature.[15]

Determination of enantiomeric excess of **21**

The enantiomeric excess was determined by ^{1}H NMR spectroscopy on a Varian Gemini 200 MHz spectrometer in $CDCl_3$ solution utilising Pr(hfc)$_3$ as the shift reagent. Using this method, a splitting was observed for both of the ester methyl singlets with the one at higher field being measured.[22] HPLC studies were performed on a Varian Star System using a Chiralacel OD column eluting with ^{i}PrOH: hexane 1:99 v/v at 0.7 ml/minute. These agreed with the NMR results, with the (R) enantiomer eluting first,[23] as confirmed by optical rotation measurements compared to the literature values.[15]

Cyclic voltammetry titration studies

Standard solutions of ligands **17**, **18** and **26** were prepared at 10^{-4} M in dry acetonitrile containing 10^{-2} M tetrabutylammonium hexafluorophosphate. A degassed 5 ml sample of this solution was employed in the subsequent studies. To these standard samples were added sequential aliquots (25 μL, 0.5 equiv.) of a 10^{-2} M solution of palladium acetate in dry acetonitrile containing 10^{-2} M tetrabutylammonium perchlorate. The cyclic voltammogram was recorded in each case with internal resistance (iR) compensation and corrected versus ferrocene/ferrocenium$^+$ as $E^{1/2}$=+0.36V. Additions were recorded until no further change in the trace could be observed.

Crystal data: $C_{16}H_{21}FeNO_2S$ (**16**), M=347.25, T=150 K, monoclinic, space group $P2_1$, a=7.2999(4), b=8.6752(4), c=12.5985(7) Å, β=99.392(3)°, U=787.14(7) Å^3, Z=2, D_x=1.465 g cm^{-3}, graphite-monochromated Mo–K_α radiation, λ=0.71073 Å, μ=10.9 cm^{-1}, amber crystal of 0.4×0.4×0.18 mm; 5568 reflections with 2θ<58° (2886 unique, 2823 'observed' with I>2σ(I), R_{int}=0.032) were measured with Siemens CCD area detector; integration absorption correction (5 faces indexed, $T_{min,max}$=0.683, 0.851), full-matrix least squares refinement (non-H atoms anisotropic, H isotropic, 275 variables) against F^2 (using SHELXL-93 software[24]) converged at wR(F^2, all data)=0.060, R(F, obs. data)=0.024; residual $\Delta\rho_{min,max}$=0.22, −0.25 eÅ^{-3}. The absolute configuration was determined by refining the Flack parameter,[25] which converged to −0.004(14) (*cf.* 0 for the correct and +1 for the inverted absolute structure); anomalous scattering corrections for all atoms were considered. Atomic coordinates, bond distances and angles have been deposited at the Cambridge Crystallographic Data Centre.

Acknowledgements

We are grateful to the EPSRC for funding this work (Grant # GR/L02753 to A. C.). We would like to thank Dr J. C. Anderson and Mr S. J. Thorpe (Chemistry Department, University of Sheffield) and Mr L. Lauchlan (Chemistry Department, University of Durham) for performing the HPLC analysis on samples of **21**.

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(*Received in UK 1 May 1997*)