

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 postulate⁴ 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 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}



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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-Lcysteine 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 (PPh₃, Et₃N, CCl₄)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 methanol¹³ was, however, extremely clean, giving oxazolines 17 and 18 in 70% and 72% yields, respectively.



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.



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



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. Enant	tioselectivity in	n palladium	allylic s	substitution	reactions	using	oxazolines	17	and	18	ŝ
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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 ¹H-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 C₂-symmetrical bis-oxazolines based on the ferrocene core, which would provide two identical catalytic sites per molecule of ligand.¹⁷

The route to the C₂-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 hydroxide¹³ both afforded product **26** in very poor yields. The use of Appel conditions¹² did, however, provide the requisite homochiral bis-oxazoline **26** in reasonable yield.





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.





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 measurements⁴ An identical study was therefore performed. The titration of a standard solution of palladium acetate

Entry	Solvent a	Ligand	Time (h)	Yield (%) ^b	ee ^c of (+) 21 (%) ^d
1	THF	18	48	98	76
2	CH ₂ Cl ₂	18	36	98	93
3	Toluene	18	48	93	74
4 e	CH ₂ Cl ₂	18	_ 36	97	85
5 f	THF	26	_36	70	76
6 f	CH ₂ Cl ₂	26	24	86	82
7	CH ₂ Cl ₂	26	36	93	91

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

a) All reactions 0.4 mM in acetate 19 unless stated otherwise. b) Yield of analytically pure product after column chromatography. c) Determined by ¹H-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	$E_1^{1/2} / mV$	E2 ^{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 reported¹⁹ 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

¹H NMR spectra were obtained on a Varian 400 at 399.96 MHz, ¹³C 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 (MgSO₄) 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; $\delta_{\rm H}$ (CDCl₃) 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); $\delta_{\rm C}$ (CDCl₃) 15.5, 35.1, 50.4, 64.9, 68.0, 68.2, 69.8, 70.6, and 150.9; $\nu_{\rm max}$ (KBr)/cm⁻¹ 1633, 1612, 1541, 1104, and 825; m/z (DCI) 333 (MH⁺, 100%); Analysis calculated for C₁₅H₁₉NFeO₂S; C 54.07, H 5.75, N 4.20. Observed; C 53.99, H 5.83, N 3.87; [α]_D²⁰=-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 (MgSO₄) 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; $\delta_{\rm H}$ (CDCl₃) 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); $\delta_{\rm C}$ (CDCl₃) 15.7, 30.1, 30.9, 51.6, 65.8, 68.29, 68.2, 69.8, 70.6, 75.5, and 171.5; $v_{\rm max}$ (KBr)/cm⁻¹ 1624, 1543, 1299, and 826; m/z (DCI) 348 (MH⁺, 100%); Analysis calculated for C₁₆H₂₁NFeO₂S; C 55.37, H 6.10, N 4.03. Observed; C 55.21, H 6.09, N 3.79; [α]_D²⁰=+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 $(2 \times 50 \text{ ml})$. The organic phase was dried (MgSO₄) 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 $(3 \times 25 \text{ ml})$, the organic fractions combined, dried (MgSO₄) 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 $\delta_{\rm H}$ (CDCl₃) 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); $\delta_{\rm C}$ (CDCl₃) 16.2, 39.1, 66.1, 68.9, 69.0, 69.7, 69.8, 70.3, 70.4, 71.5 and 167.3; v_{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 $\delta_{\rm H}$ (CDCl₃) 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); $\delta_{\rm C}$ (CDCl₃) 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; $\nu_{\rm max}$ (KBr)/cm⁻¹ 1650, 1535, and 835; m/z (DCI) 330 (MH⁺, 100%); Analysis calculated for C₁₆H₁₉NFeOS; C 58.37, H 5.82, N 4.25. Observed; C 58.15, H 5.74, N 3.93; [α]_D²⁰–92 (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 (MgSO₄) 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. $\delta_{\rm H}$ (CDCl₃) 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); $\delta_{\rm C}$ (CDCl₃) 15.5, 30.6, 30.9, 51.1, 64.3, 62.4, 71.5, 77.4 and 170.5; $\nu_{\rm max}$ (KBr)/cm⁻¹ 3320, 2905, 1680, and 1597; m/z (DCI) 508 (MH⁺, 100%); Analysis calculated for C₂₂H₃₂N₂FeO₄S₂; C 51.97, H 6.34, N 5.51. Observed; C 51.83, H 6.38, N 5.42; $[\alpha]_{\rm D}^{20}$ =+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 (MgSO₄) 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 (CDCl₃) 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); $\delta_{\rm C}$ (CDCl₃) 115.5, 30.7, 35.3, 65.7, 70.5, 70.7, 71.8, 72.0, and 165.3; $v_{\rm max}$ (CH₂Cl₂)/cm⁻¹ 2928, 2856, and 1656; m/z (DCI) 473 (MH⁺, 100%); HRMS calculated for C₂₂H₂₈FeN₂O₂S₂ 472.0975 found 472.0970; [α]_D²⁰=-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 $[\{Pd(\eta_3-C_3H_5)Cl\}_2]$ (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 (MgSO₄) 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 $[\{Pd(\eta_3-C_3H_5)Cl\}_2]$ (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 (MgSO₄) 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 ¹H NMR spectroscopy on a Varian Gemini 200 MHz spectrometer in CDCl₃ 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 ¹PrOH: 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 μ L, 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: C₁₆H₂₁FeNO₂S (**16**), M=347.25, T=150 K, monoclinic, space group P2₁, *a*=7.2999(4), *b*=8.6752(4), *c*=12.5985(7) Å, β =99.392(3)°, U=787.14(7) Å³, Z=2, D_x=1.465 g cm⁻³, graphitemonochromated 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 20<58° (2886 unique, 2823 'observed' with I>2 σ (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 F² (using SHELXL-93 software²⁴) converged at wR(F², 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.

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References

- (a) Seyden-Penne, J. Chiral Auxiliaries and Ligands In Asymmetric Synthesis; Wiley: New York, 1995. (b) Heathcock, C. Acc. Chem. Res., 1986, 15.
- For leading monographs see; (a) Bosnich, B. Asymmetric Synthesis, NATO ASI Series 6, 103, Martins Nijhoft: Dordrecht, 1986, Chp.3. (b) Morrison, J. D. Asymmetric Synthesis, vol 1-5, Academic Press: New York, 1984.
- (a) Beer, P. D. in *Molecular Engineering for Advanced Materials*, NATO ASI Series 456, Becher, J.; Schaumburg, K. (Eds.) Kluwer Academic Press, **1995**, 99. (b) Hansen, T. K.; Jørgensen, T.; Stein, P. C.; Becher, J. J. Org. Chem., **1992**, 57, 6403.
- 4. Chesney, A.; Bryce, M. R. Tetrahedron: Asymmetry, 1996, 7, 3247.
- For reviews see; (a) Tongi, A.; Venanzi, L. Angew. Chem. Int. Ed. Engl., 1993, 33, 497. (b) Pfaltz, A. Acc. Chem. Res., 1993, 26, 339. (c) Reuman, M.; Meyers, A. I. Tetrahedron, 1985, 41, 837.
- (a) Richards, C. J.; Mulvaney, A. W. Tetrahedron: Asymmetry, 1996, 7, 1419. (b) Zhang, W.; Adachi, Y.; Hirao, T.; Ikeda, I. Tetrahedron: Asymmetry, 1996, 7, 451. (c) Sammakia, T.; Latham, H. A. J. Org. Chem., 1995, 60, 6002. (d) Richards, C. J.; Damalidis, T.; Hibbs, D. E.; Hursthouse, M. B. Synlett., 1995, 74. (e) Nishibayashi, Y.; Uemura, S. Synlett., 1995, 79. (f) Nishibayashi, Y.; Segawa, K.; Takada, H.; Ohe, K.; Uemura, S. Chem. Commun., 1996, 847. (g) Sammakia, T.; Latham, H. A.; Schaad, D. R. J. Org. Chem., 1995, 60, 10.
- 7. Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. J. Am. Chem. Soc., 1989, 111, 6301.
- 8. Connely, N. G.; Geiger, W. E. Adv. Organomet. Chem., 1984, 23, 1 and references cited therein.
- For some representative examples see; (a) Newman, L. M.; Williams, J. M. J.; McCague, R.; Potter, G. A. Tetrahedron: Asymmetry, 1996, 7, 1597. (b) Langer, T.; Janssen, J.; Helmchen, G. Tetrahedron: Asymmetry, 1996, 7 1599. (c) Allen, J. V.; Bower, J. F.; Williams, J. M. J. Tetrahedron:

Asymmetry, **1994**, 5, 1895. (d) Allen, J. V.; Coote, S. J.; Dawson, G. J.; Frost, C. G.; Martin, C. J.; Williams, J. M. J. J. Chem. Soc. Perkin Trans. 1, **1994**, 2065. (e) Allen, J. V.; Dawson, G. J.; Frost, C. G.; Williams, J. M. J.; Coote, S. J. Tetrahedron, **1994**, 50, 799. (f) Dawson, G. J.; Frost, C. G.; Williams, J. M. J.; Coote, S. J. Tetrahedron Lett., **1993**, 34, 7793. (g) Dawson, G. J.; Frost, C. G.; Williams, J. M. J.; Coote, S. J. Tetrahedron Lett., **1993**, 34, 3149.

- 10. Vögel, D.; Pohm, M. Monatsh. Chem., 1952, 83, 541.
- 11. Ferrocene acid chloride was prepared by the action of oxalyl chloride on ferrocene carboxylic acid in anhydrous dichloromethane containing catalytic dimethylformamide (cf. Arimoto, F. S.; Haven, A. C. J. Am. Chem. Soc., 1955, 77, 6295).
- 12. Vorbruggen, H.; Krolokliewicz, K. Tetrahedron Lett., 1981, 22, 4471.
- Denmark, S. E.; Nakajima, N.; Nicaise, O. J.-C.; Faucher, A.-M.; Edwards, J. P. J. Org. Chem., 1995, 60, 4884.
- 14. Auburn, P. R.; Mackenzie, P. B.; Bosnich, B. J. Am. Chem. Soc., 1985, 107, 2033.
- 15. For a study of binding factors influencing the enantiomeric excess obtained in a variety of systems see: Trost, B. M.; Breit, B.; Organ, M. G. *Tetrahedron Lett.*, **1994**, *35*, 5817 and references cited therein.
- 16. Leutenegger, V.; Umbricht, G.; Fahrini, C.; von Matt, P.; Pfaltz, A. Tetrahedron, 1992, 48, 2143.
- Bis-oxazolines have recently been extensively employed in several catalytic reactions: For some representative examples see (a) Bölm, C. Angew. Chem., Int. Ed. Engl., 1991, 30, 542. (b) Reiser, O. Angew. Chem., Int. Ed. Engl., 1993, 32, 547. (c) Evans, D.A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. J. Am. Chem. Soc., 1993, 115, 5328. (d) Evans, D. A.; Miller, S. J.; Leckta, T. J. Am. Chem. Soc., 1993, 115, 6460. (e) von Matt, P.; Pfaltz, A. Angew. Chem., Int. Ed. Engl., 1993, 32, 566.
- 18. Lorkowski, H.; Pannier, R.; Wende, A. J. Prakt. Chem., 1967, 35, 149.
- 19. (a) Seyferth, D.; Hames, B. W.; Rucker, T. G.; Cowie, M.; Raymond, S. D. Organometallics, 1983, 2, 472. (b) Cowie, M.; Dickson, R. S. J. Organomet. Chem., 1987, 326, 269.
- (a) Akabori, S.; Kumagai, T.; Shirahige, T.; Sato, S.; Kawazoe, K.; Tamura, C.; Sato, M. Organometallics, 1987, 6, 2105. (b) Sato, M.; Sekino, M.; Akabori, S. J. Organomet. Chem., 1988, 344, C31. (c) Sato, H.; Suzuki, K.; Katada, M.; Akabori, S. Bull. Chem. Soc. Jpn., 1989, 62, 3828. (d) Medina, J. C.; Goodnow, T. T.; Rojas, M. T.; Atwood, J. L.; Lynn, B. C.; Kaifer, A. E.; Gokel, G. W. J. Am. Chem. Soc., 1992, 114, 10583.
- 21. Miller, S. R.; Gustowski, D. A.; Chen, Z. C.; Gokel, G. W.; Echegoyen, L.; Kaifer, A. E. Anal. Chem., 1988, 60, 2021.
- 22. Sullivan, G. R. Top. Stereochem., 1987, 10, 287.
- 23. Williams, J. M. J. University of Bath, U.K., personal communication.
- 24. Sheldrick, G. M. SHELXL-93, Program for the refinement of crystal structures, University of Göttingen, Germany, 1993.
- 25. Flack, D. Acta Crystallogr. Sect. A, 1983, 39, 876.

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