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Preparation of Novel Sulfur and Phosphorus Containing Oxazolines as Ligands for Asymmetric Catalysis

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Abstract: The preparation of enantiomerically pure ligands which contain both an oxazoline group and an additional sulfur or phosphorus donor atom are described. Methylthiomethyl, *o*-thioanisyl and thienyl oxazolines have been prepared in one step, and *o*-diphenylphosphinophenyl oxazolines have been prepared in two steps in good yields from commercially available starting materials.

INTRODUCTION

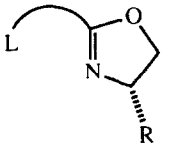
Almost twenty years ago, Meyers reported the use of enantiomerically pure oxazolines as stoichiometric auxiliaries for asymmetric reactions.[1] The stereochemical control exerted by oxazolines in auxiliary based reactions is generally excellent and has found numerous valuable applications in asymmetric synthesis.[2]

The use of enantiomerically pure oxazolines for asymmetric catalysis is more recent. In 1989, several groups reported the use of pyridyl oxazolines as ligands for catalytic asymmetric hydrosilylation.[3] These reports firmly established the good stereochemistry-controlling properties of oxazolines as ligands in metal mediated catalysis.

Subsequently, a series of C_2-symmetric bis-oxazolines appeared from a number of groups and were used to great effect for various catalytic processes.[4] Catalysts derived from these bis-oxazolines rely upon the C_2-symmetric nature of the ligand to reduce the number of stereochemical permutations within the catalytic ensemble, and thereby afford high levels of enantiocontrol. A strategy that has evidently been successful.[5]

However, our interests were concerned with the preparation of ligands which exploit the stereochemistry-controlling properties of the oxazoline, whilst incorporating a secondary donor atom.

Auxiliary Donor Ligand



Stereochemistry-controlling Oxazoline Moiety

The secondary donor atom may be tailored to the catalytic system to provide;

i) Modified binding properties
ii) Different steric environment
iii) Non-equivalent electronic behaviour of the donor atoms.

RESULTS AND DISCUSSION

Sulfur containing oxazoline ligands

We wished to prepare enantiomerically pure oxazoline ligands which contained a sulfur donor atom. We envisioned three different sulphur groups; an alkyl sulphide,[6] an aryl sulphide,[7] and a sulfur contained within a thiophene ring.[8] Thus, three electronically and sterically distinct ligand types were considered, **5**, **6** and **7**.

These ligands were prepared by the reaction of the appropriate nitriles with homochiral amino alcohols affords the homochiral oxazoline in a one step process catalysed by zinc chloride in chlorobenzene at reflux for 48 hours.[9] Thus, the reaction of nitriles **1**, **2**, and **3** with the homochiral alcohols **4a-f**[10] afforded the corresponding oxazolines **5a-e**, **6a-e** and **7b-f** in good yields (Table 1).

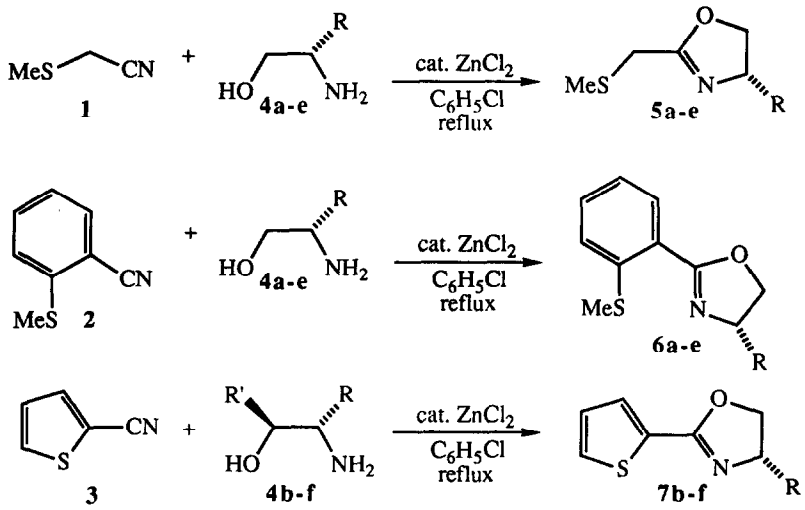


Table 1: Preparation sulfur-containing oxazolines

Nitrile	*Amino alcohol*	*R*	*R'*	*Oxazoline*	*Yield (%)*
1	**4a**	Me	H	**5a**	82
1	**4b**	$PhCH_2$	H	**5b**	62
1	**4c**	^{i}Pr	H	**5c**	66
1	**4d**	Ph	H	**5d**	73
1	**4e**	^{t}Bu	H	**5e**	62
2	**4a**	Me	H	**6a**	60
2	**4b**	$PhCH_2$	H	**6b**	42
2	**4c**	^{i}Pr	H	**6c**	69
2	**4d**	Ph	H	**6d**	58
2	**4e**	^{t}Bu	H	**6e**	53
3	**4b**	$PhCH_2$	H	**7b**	73
3	**4c**	^{i}Pr	H	**7c**	88
3	**4d**	Ph	H	**7d**	79
3	**4e**	^{t}Bu	H	**7e**	74
3	**4f**	Me	Ph	**7f**	91

Phosphorus containing oxazoline ligands

The sulfur containing oxazoline ligands provide a donor ligand which behaves as a small π-acceptor (or as a π-donor in the case of the electron rich thiophene ligand). In order to dramatically alter steric effects, whilst maintaining similar electronic properties in the donor ligand, we decided to explore the preparation of the phosphorus containing oxazoline ligands **10**.[11]

These ligands were prepared by a two step process. *o*-Fluorobenzonitrile **8** was readily converted into the corresponding oxazoline **9a-e** upon treatment with an amino alcohol using catalytic zinc chloride in refluxing chlorobenzene. The fluoro-oxazolines **9a-e** were further converted into the 2-(*o*-diphenylphosphinophenyl)oxazolines **10a-e** on treatment with potassium diphenylphosphide in THF at reflux (Table 2).[12] Ligands **10a-e** could be isolated as air stable solids by column chromatography, although on exposure to air in solution, slow oxidation to the corresponding phosphine oxides occurs over a period of several weeks.

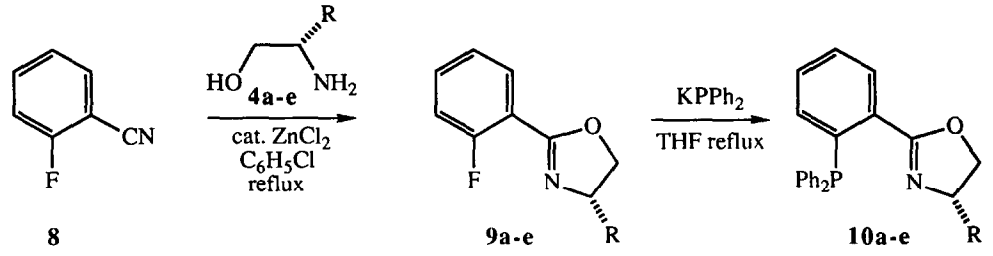
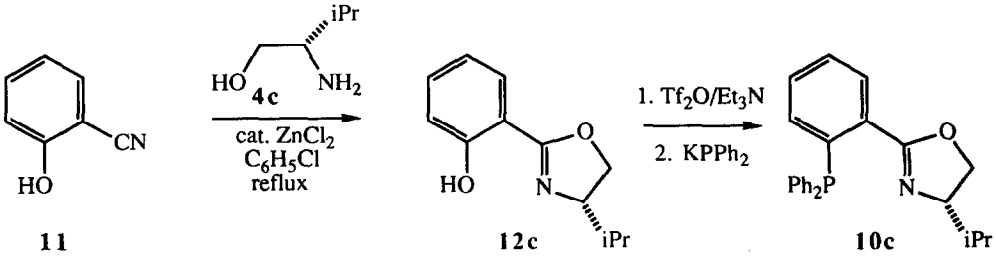


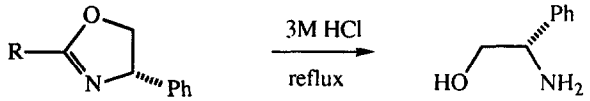
Table 2: Preparation of 2-*o*-(diphenylphosphino)phenyloxazolines **10a-e**

Amino alcohol	*R*	*F-oxazoline*	*Yield (%)*	*P-oxazoline*	*Yield (%)*
4a	Me	**4a**	47	**10a**	80
4b	$PhCH_2$	**4b**	48	**10b**	76
4c	^{i}Pr	**4c**	46	**10c**	76
4d	Ph	**4d**	49	**10d**	84
4e	^{t}Bu	**4e**	56	**10e**	92

An alternative approach to the preparation of ligand **10c** is from *o*-cyanophenol **11**, which is converted into the oxazoline **12c** on reaction with valinol **4c** according to the procedure of Bolm in 54% yield.[9] Conversion into the triflate and reaction of the crude product with potassium diphenylphosphide afforded the product **10c** in 51% yield (from **12c**).

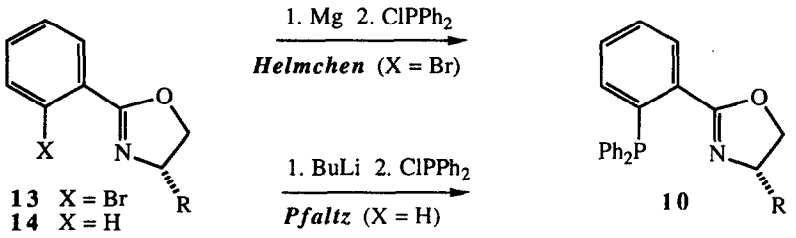


The enantiomeric purity of the oxazolines derived from phenylglycinol **4d** was determined indirectly. Hydrolysis of ligands **5d**, **6d**, **7d** and **10d** under acidic conditions liberated (S)-phenylglycinol **4d**, $[\alpha]^D$ = +32, c=0.5, CH_2Cl_2). In each case, comparison of the optical rotation with an authentic sample of (S)-phenylglycinol confirmed that there had been no loss of stereochemical integrity during the formation of oxazoline. Since the 4-phenyl substituted ligands were considered to be the most prone to potential racemisation, it was assumed that all of the other ligands were likewise enantiomerically pure.



5, 6, 7 or 10d **4d**

Since this work was initiated, Helmchen and Pfaltz have also prepared ligands of type **10**, using an alternative approach. Helmchen converted the bromo-oxazoline **13** into the Grignard reagent, and then reacted it with chlorodiphenylphosphine, which affords the same product **10c** in 30% yield.[13] Similarly, Pfaltz converted the phenyloxazoline **14** into the *o*-lithiooxazoline by orthometallation, and reaction with chlorodiphenylphosphine also affords the product **10c** in 35% yield.[14]



13 X = Br
14 X = H

10

Summary

New ligands which combine the stereochemistry controlling properties of the oxazoline moiety with an additional donor atom have been synthesised. This Paper deals with sulfur and phosphorus donor atoms, although other possibilities are currently being considered.[15]

The electronic environment of the sulfur donor atom has been varied form alkyl sulphide to aryl sulphide and even to a sulfur contained within a thiophene ring. Thus, these ligands provide the opportunity to probe electronic effects in transition metal promoted and catalysed reactions. So far, the use of these ligands for asymmetric palladium catalysed reactions has yielded very high enantioselectivities. Applications as ligands in other catalytic systems are currently being pursued.

EXPERIMENTAL SECTION

General Experimental

Commercially available solvents and reagents were used throughout without further purification, except for those detailed below which were purified as described. 'Light petroleum' refers to the fraction of petroleum ether boiling between 40°C and 60°C, and was distilled through a 36cm Vigreux column before use. Diethyl ether was dried by standing over sodium wire for several days. THF was distilled from sodium benzophenone ketyl under nitrogen, prior to use. Dichloromethane was distilled from phosphorus pentoxide. DMF was dried by stirring over calcium hydride for 15h, decanted, and distilled under reduced pressure before storing over 4Å molecular sieves under nitrogen.

Analytical thin layer chromatography was carried out using aluminium backed plates coated with Merck Kieselgel 60 GF_{254}. Plates were visualised under UV light (at 254 and/or 360 nm) or by staining with

phosphomolybdic acid reagent, followed by heating. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Sorbsil C 60 silica gel. Pressure was applied at the column head with hand bellows. Samples were applied pre-absorbed on silica or as a saturated solution in an appropriate solvent.

Infra red spectra were recorded in the range 4000-600 cm^{-1} using a Nicolet FT-205 spectrometer, with internal calibration. Spectra were recorded as solutions in chloroform, thin films or as a nujol mull. Elemental analyses were carried out on a Perkin Elmer 2400 Elemental Analyser. ^{1}H and ^{13}C NMR spectra were recorded using Bruker AC-250 and Bruker WH-400 (SERC NMR Spectroscopy Centre, Warwick) instruments. High and low resolution mass spectra were recorded on a Kratos MS80 instrument or on a VG Analytical ZAB-E instrument (SERC mass spectrometry service Swansea). Melting points were measured on an Electrothermal digital melting point apparatus and are uncorrected. Optical rotations were determined on an Optical Activity AA100 polarimeter.

General procedure for preparation of 1,3-oxazolines 5a-e, 6a-e, 7b-f and 9a-e

In a 50ml Schlenk flask, zinc chloride (68mg, 0.5 mmol) is melted under high vacuum and cooled under nitrogen. After cooling to room temperature, chlorobenzene (30ml) was added followed by nitrile **1, 2** or **3** (10 mmol) and the amino alcohol **4a-e** (13 mmol). The mixture was heated under reflux for 48 hours. The solvent was removed under reduced pressure to give an oily residue, which was dissolved in dichloromethane (30ml). The solution was extracted three times with water (20ml) and the aqueous phase with dichloromethane (30ml). The combined organic phases were dried with sodium sulphate, and the solvent removed *in vacuo*. The residue was purified by flash chromatography (light petroleum/ether 3:1) to afford the title compounds.

(4S)-2-methylthiomethyl-4-methyl-1,3-oxazoline (5a). (82%) as a colourless oil. (found M^+, 145.0561. $C_6H_{11}NOS$ requires M^+, 145.0561). $[\alpha]_D^{25}$ -68.8 (c=1.96, $CHCl_3$). υ_{max} / cm^{-1} 1661. δ_H (250 MHz, $CDCl_3$) 1.25 (d, 3H, J = 6.6Hz, $CHCH_3$), 2.19 (s, 3H, SCH_3), 3.23 (s, 2H, SCH_2) 3.83 (t, 1H, J = 8.0Hz, CHO), 4.18 (m, 1H, CHN), 4.39 (t, 1H, J = 8.0Hz, CHO). δ_C (62.5 MHz, $CDCl_3$) 15.9 (SCH_3), 21.4 ($CHCH_3$), 30.1 (SCH_2), 61.7 (CHN), 77.1 (CH_2O), 164.0 (C=N).

(4S)-4-benzyl-2-methylthiomethyl-1,3-oxazoline (5b). (62%) as a colourless oil. (found M^+, 221.0881. $C_{12}H_{15}NOS$ requires M^+, 221.0874). $[\alpha]_D^{25}$ -30.0 (c=1.77, $CHCl_3$). υ_{max} / cm^{-1} 1658. δ_H (250 MHz, $CDCl_3$) 2.18 (s, 3H, SCH_3), 2.68 (dd, 1H, J = 8.4, 13.7Hz, CHPh), 3.09 (dd, 1H, J = 5.2, 13.7Hz, CHPh), 3.23 (s, 2H, SCH_2), 4.01 (t, 1H, J = 7.4, 8.3Hz, CH-O), 4.29 (t, 1H, J = 8.3, 9.3Hz, CH-O), 4.39 (m, 1H, CH-N), 7.18-7.35 (m, 5H, ArH). δ_C (62.5 MHz, $CDCl_3$) 16.0 (SCH_3), 30.1 (SCH_2), 41.7 (CH_2Ph), 67.5 (CH_2O), 72.3 (CHN), 126.6 (ArC), 128.6 (ArC), 129.2 (ArC), 137.8 (ArC), 165.0 (C=N).

(4S)-4-isopropyl-2-methylthiomethyl-1,3-oxazoline (5c). (66%) as a colourless oil. (found M^+, 173.0876. $C_8H_{15}NOS$ requires M^+, 173.0874). $[\alpha]_D^{25}$ -43.7 (c=0.8, $CHCl_3$). υ_{max} / cm^{-1} 1660. δ_H (250 MHz, $CDCl_3$) 0.65 (d, 3H, J = 6.8Hz, $CHCH_3$), 0.73 (d, 3H, J = 6.8Hz, $CHCH_3$), 1.53 (m, 1H, $CH(CH_3)_2$), 1.95 (s, 3H, SCH_3), 3.00 (s, 2H, SCH_2), 3.66 (m, 1H, CHN), 3.74 (t, 1H, J = 7.0Hz, CHO), 4.05 (t, 1H, J = 7.0Hz, CHO). δ_C (62.5 MHz, $CDCl_3$) 15.6 (SCH_3), 17.8 ($CHCH_3$), 18.4 ($CHCH_3$), 29.6, (SCH_2), 32.3 ($CH(CH_3)_2$), 70.2 (OCH_2), 72.0 (NCH), 163.9 (C=N).

(4S)-2-methylthiomethyl-4-phenyl-1,3-oxazoline (5d). (73%) as a colourless oil. (found M^+, 207.0718. $C_{11}H_{13}NOS$ requires M^+, 207.0718). $[\alpha]_D^{25}$ -75.0 (c=1.24, $CHCl_3$). υ_{max} / cm^{-1} 1658. δ_H (250 MHz, $CDCl_3$) 2.14 (s, 3H, SCH_3), 3.34 (s, 2H, SCH_2), 4.15 (t, 1H, J = 8.3Hz, CHH), 4.69 (dd, 1H, J = 8.3, 10.1Hz, CHH), 5.24 (t, 1H, J = 9.8Hz, CHN), 7.20-7.34 (m, 5H, ArH). δ_C (62.5 MHz, $CDCl_3$) 16.2 (SCH_3), 30.0 (SCH_2), 69.7 (CHN), 75.1 (CH_2O), 126.5 (ArC), 127.6 (ArC), 128.7 (ArC), 142.0 (ArC), 166.2 (C=N).

(4S)-4-^{t}butyl-2-methylthiomethyl-1,3-oxazoline (5e). (62%) as a colourless oil. (found M^+, 187.1029. $C_9H_{17}NOS$ requires M^+, 187.1031). $[\alpha]_D^{25}$ -50.0 (c=0.86, $CHCl_3$). υ_{max} / cm^{-1} 1664. δ_H (250 MHz, $CDCl_3$) 0.94 (s, 9H, $C(CH_3)_3$), 2.15 (s, 3H, SCH_3), 3.24 (s, 2H, SCH_2), 3.87 (t, 1H, J = 7.5Hz, CHN), 3.91 (t, 1H, J = 8.5Hz, CHO), 4.22 (t, 1H, J = 8.7, 10.1Hz, CHO). δ_C (62.5 MHz, $CDCl_3$) 16.0 (SCH_3), 25.8 (3 X CH_3), 69.1 (CH_2O), 76.0 (CHN), 164.3 (C=N).

(4S)-2-((2-methylthio)phenyl)-4-methyl-1,3-oxazoline (6a). (60%) as a colourless oil. (found M^+, 207.0718. $C_{11}H_{13}NOS$ requires M^+, 207.0718). $[\alpha]_D^{25}$ -21.4 (c=0.28, $CHCl_3$). υ_{max} / cm^{-1} 1644. δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, J = 6.44Hz, CH_3CH-), 2.44 (3H, s, CH_3S-), 3.91 (1H, m, CHH'O-), 4.45 (1H, m, CHH'O-), 4.49 (1H, m, CHN), 7.11-7.81 (4H, m, ArH). δ_C (100.6 MHz, $CDCl_3$) 15.6 (CH_3S-), 21.5 (CH_3CH-), 62.6 (CHN), 73.0 (CH_2O), 123.4 (ArCH), 124.0 (ArCH), 124.9(ArC), 130.1 (ArCH), 130.7 (ArCH), 140.6 (ArC), 162.1 (C=N). *m/z* (EI) 207, 192, 152.

(4S)-4-benzyl-2-((2-methylthio)phenyl)-1,3-oxazoline (6b). (42%) as a colourless solid. M.p. 68-69 °C . (found: C, 72.4; H, 5.9; N, 4.9. $C_{17}H_{17}NOS$ requires C, 72.1; H, 6.0; N, 4.9%). $[\alpha]_D^{25}$ +18.7 (c=0.16, $CHCl_3$). υ_{max} / cm^{-1} 1640. δ_H (400 MHz, $CDCl_3$) 2.47 (3H, s, CH_3S-), 2.74 (1H, dd, J = 9.1, 13.7Hz, PhCHH'-), 3.31 (1H, dd, J = 5.0, 13.7Hz), PhCHH'-), 4.10 (1H, dd, J = 7.1, 8.4Hz, -OCHH'-), 4.27 (1H, dd J = 8.4, 9.2Hz, -OCHH'-), 4.69 (1H, m, CHN), 7.12-7.81 (9H, m, ArH). δ_C (100 MHz, $CDCl_3$) 15.7 (CH_3S-), 41.7 ($PhCH_2$), 68.6 (CHN), 70.7 (CH_2O), 123.4 (ArCH), 124.0 (ArCH), 126.3 (ArCH), 124.7 (ArC), 128.4 (ArCH), 129.2 (ArCH), 130.1 (ArCH), 130.8 (ArCH), 137.9 (ArCH), 140.8 (ArC), 162.7 (C=N). *m/z* (EI) 283, 268, 192.

(4S)-4-isopropyl-2-((2-methylthio)phenyl)-1,3-oxazoline (6c). (69%) as a colourless solid. M.p. 47 - 48 °C (found M^+, 235.1030. $C_{13}H_{17}NOS$ requires M^+, 235.1030). $[\alpha]_D^{25}$ -72.2 (c=0.18, $CHCl_3$). υ_{max} / cm^{-1} 1649. δ_H (400 MHz, $CDCl_3$) 0.95 (3H, d, J = 6.8Hz, CH_3CH-), 1.06 (3H, d, J = 6.7Hz, CH_3CH-), 1.85 (1H, m, -$CHMe_2$), 2.44 (3H, s, CH_3S-), 4.09 (apparent t, 1H, J = 7.7Hz, CHH'O-), 4.20 (1H, m, CHN), 4.35 (1H, dd, J = 7.9, 9.5Hz, CHH'O), 7.11-7.79 (4H, m, ArH). δ_C (100 MHz, $CDCl_3$) 15.7 (CH3S-), 18.1 (CH_3CH-), 18.8 (CH_3CH-), 32.8 ($CHMe_2$), 69.3 (CH_2O-), 73.3 (CHN), 123.3 (ArC), 124.0 (ArC), 125.0 (ArC), 129.9 (ArCH), 130.6 (ArCH), 140.8 (ArC), 162.0 (C=N). *m/z* (EI) 235, 220, 192.

(4S)-2-((2-methylthio)phenyl)-4-phenyl-1,3-oxazoline (6d). (58%) as a colourless crystalline solid. M.p. 72 - 73 °C . (Found: C, 71.5; H, 5.5; N, 5.2. $C_{16}H_{15}NOS$ requires C, 71.4; H, 5.6; N, 5.2%) (found M^+, 269.0873. $C_{16}H_{15}NOS$ requires M^+, 269.0874) . $[\alpha]_D^{25}$ +100 (c=0.12, $CHCl_3$). υ_{max} / cm^{-1} 1638. δ_H (250 MHz, $CDCl_3$) 2.46 (3H, s, CH_3S-), 4.20 (1H, t, J = 8.2 Hz, CHN), 4.75 (1H, dd, J = 8.2, 10.1Hz, CHH'O), 5.51 (1H, dd, J = 8.2, 10.1Hz, CHH'O), 7.14 - 7.91 (9H, m, ArH). δ_C (62.5 MHz, $CDCl_3$) 15.8 (CH_3S), 70.7 (CHN), 74.0 (CH_2O), 124.3 (ArCH), 126.6 (ArCH), 128.6 (ArCH), 131.0 (ArCH), 137.0 (ArC), 142.0 (ArC), 159.5 (C=N). *m/z* (EI) 269, 254, 151.

(4S)-4-^{t}butyl-2-((2-methylthio)phenyl)-1,3-oxazoline (6e). (53%) as a colourless crystalline solid. M.p. 67.5 - 68.5 °C . (found M^+, 249.1187. $C_{14}H_{19}NOS$ requires M^+, 249.1187). $[\alpha]_D^{25}$ -121.1 (c=0.38, $CHCl_3$). υ_{max} / cm^{-1} 1651(C=N). δ_H (400 MHz, $CDCl_3$) 0.98 (9H, s, $C(CH_3)_3$), 2.44 (3H, s, SCH_3), 4.15 (1H, m, CHN), 4.20 (1H, m, CHO), 4.26 (1H, dd, J = 7.7, 9.4 Hz, CHO), 7.11-7.78 (4H, m, ArH). δ_C (100 MHz, $CDCl_3$) 15.8 (SCH_3), 25.7 (CH_3 x 3), 33.9 ($C(CH_3)_3$), 67.7 (CH_2O), 77.0 (CHN), 123.3 (ArCH), 124.0 (ArCH), 125.0 (ArC), 129.0 (ArCH), 130.6(ArCH), 141.0 (ArC), 161.9(C=N). *m/z* (EI) 249, 234, 192.

(4S)-4-benzyl-2-(2-thienyl)-1,3-oxazoline (7b). (73%) as a colourless crystalline solid. M.p. 42 - 44 °C. (found M^+, 243.0725. $C_{14}H_{13}NOS$ requires M^+, 243.0718). $[\alpha]_D^{25}$ +26.0 (c=0.5, $CHCl_3$). υ_{max} / cm^{-1} 1651. δ_H (400 MHz, $CDCl_3$) 2.70 (1H, dd, J = 9.1, 13.7 Hz, CHH'Ph), 3.25 (1H, dd J = 4.8, 13.7 Hz, CHH'Ph), 4.13 (1H, dd, J=7.3, 8.7Hz, CHH'O), 4.32 (1H, t, J = 8.7 Hz, CHH'O), 4.52-4.60 (1H, m, CHN), 7.06-7.08 (1H, m, thienyl H), 7.20-7.32 (5H, m, ArH), 7.44-7.45 (1H, m, thienyl H), 7.57-7.59 (1H, m, thienyl H). δ_H (100 MHz, $CDCl_3$) 41.5 (CH_2-Ph), 67.9 (CHN), 72.1 (CH_2O), 126.4, 127.4, 128.4, 129.1, 129.7, 130.2, 137.7(ArC), 159.6(C=N).

(4S)-4-isopropyl-2-(2-thienyl)-1,3-oxazoline (7c). (82%) as a colourless oil. (found M^+, 195.0718. $C_{10}H_{13}NOS$ requires M^+, 195.0718). $[\alpha]_D^{25}$ -89.3 (c=0.28, $CHCl_3$). υ_{max} / cm^{-1} 1651. δ_H (400 MHz, $CDCl_3$) 0.90 (3H, d, J = 6.8 Hz, CH_3), 1.00 (3H, d, J = 6.8 Hz, CH_3), 1.84 (1H, m, $CH(CH_3)_2$), 4.05-4.15 (2H, m, CH_2O), 4.34-4.41 (1H, m, CHN), 7.05 (1H, m, thienyl H), 7.41 (1H, m, thienyl H), 7.57 (1H, m, thienyl H). δ_C (100 MHz, $CDCl_3$) 17.8(CH_3), 18.8(CH_3), 32.5($CH(CH_3)_2$), 70.2(CH_2O), 72.6(CHN), 127.4 (thienyl CH), 129.4 (thienyl CH), 129.9 (thienyl CH), 130.3(thienyl C), 158.9(C=N). *m/z* (EI) 195, 152, 124.

(4S)-4-phenyl-2-(2-thienyl)-1,3-oxazoline (7d). (79%) as a colourless crystalline solid. M.p. 78-79 °C. (Found: C, 68.4; H, 4.9; N, 6.1. $C_{13}H_{11}NOS$ requires C, 68.1; H,4.8; N, 6.1%). $[\alpha]_D^{25}$ +18.3 (c=0.6, $CHCl_3$). υ_{max} / cm^{-1} 1644. δ_H (250 MHz, $CDCl_3$) 4.26 (1H, dd, J = 8.2, 8.2 Hz, CHH'O), 4.77 (1H, dd, J = 8.3, 8.3 Hz, CHH'O), 5.36 (1H, dd, J = 8.1, 8.1 Hz, CHN), 7.10 (1H, m, thienyl H), 7.28 (5H, m, ArH), 7.47 (1H, m, thienyl H), 7.68 (1H, m, thienyl H). δ_C (63 MHz, $CDCl_3$) 70.3(CHN), 75.2(CH_2-O), 126.8 (ArCH), 127.7 (ArCH), 128.8 (ArCH), 130.1 (ArCH), 130.7 (ArCH), 142.1(ArC), 160.2(C=N). *m/z* (EI) 229, 199.

(4S)-4-^{t}butyl-2-(2-thienyl)-1,3-oxazoline (7e). (74%) as a colourless crystalline solid. M.p. 44 - 45 °C. (found M^+, 209.0868. $C_{11}H_{15}NOS$ requires M^+, 209.0874). $[\alpha]_D^{25}$ -76.5 (c=0.34, $CHCl_3$). υ_{max} / cm^{-1} 1654. δ_H (250 MHz, $CDCl_3$) 0.95 (9H, s, $C(CH_3)_3$), 4.03 (1H, dd, J = 7.4, 10.0 Hz, CHN), 4.26 (2H, m, CH_2O), 7.06 (1H, m, thienyl H), 7.43 (1H, m, thienyl H), 7.59 (1H, m, thienyl H). δ_C (62.5 MHz, $CDCl_3$) 25.9 (CH_3 x 3), 34.1 ($C(CH_3)_3$), 69.1 (CH_2O), 76.4 (CHN), 127.5 (thienyl C), 129.5 (thienyl C), 130.2 (thienyl C), 159.1 (C=N).

(4S,5R)-4-methyl-5-phenyl-2-(2-thienyl)-1,3-oxazoline (7f). (91%) as a viscous, colourless oil. (found MH^+, 244.0796. $C_{14}H_{13}NOS$ requires MH^+, 244.0796). $[\alpha]_D^{25}$ -553 (c=0.28, $CHCl_3$). υ_{max} / cm^{-1} 1651. δ_H (400 MHz, $CDCl_3$) 0.87 (3H, d, J=7.0 Hz, CH_3), 4.63 (1H, dq, J=9.7, 7.0 Hz, CH-CH_3), 5.74 (1H, d, J = 9.7 Hz, CHO), 7.11 (1H, m, thienyl H), 7.23-7.37 (5H, m, ArH), 7.49 (1H, m, thienyl H), 7.69 (1H, m, thienyl H). δ_C (100 Hz, $CDCl_3$) 17.6(CH_3), 65.5(CHN), 84.3(CHO), 126.0(ArCH), 127.5 (ArCH), 127.8 (ArCH), 128.2 (ArCH), 129.8 (ArCH), 130.3 (ArCH), 131.9 (ArC) 136.7 (ArC), 158.7 (C=N). *m/z* (EI) 244, 170, 137.

(4S)-2-(2-fluorophenyl)-4-methyl-1,3-oxazoline (9a). (47%) as a colourless oil. (found M^+, 179.0749. $C_{10}H_{10}FNO$ requires M^+, 179.0746). $[\alpha]_D^{25}$ -66.0 (c=0.8, $CHCl_3$). υ_{max} / cm^{-1} 1651. δ_H (250 MHz, $CDCl_3$) 1.37 (3H, d, J=6.4Hz, CH_3), 3.95 (1H, t, J=7.3Hz, CHO), 4.41 (2H, m, CHN and CHO), 7.10 -7.49 (3H, m, ArH), 7.84 - 7.91 (1H, m, ArH). δ_C (100 MHz, $CDCl_3$) 21.3 (CH_3), 62.1 (CHN), 73.5 (CH_2O), 116.3 (ArC), 116.5 (ArC), 123.6 (ArC), 131.0 (ArC), 132.4 (ArC), 132.5 (ArC), 163.2 (C=N)

(4S)-4-benzyl-2-(2-fluorophenyl)-1,3-oxazoline (9b). (48%) as a colourless oil. (found M^+, 255.1064. $C_{16}H_{14}FNO$ requires M^+, 255.1059). $[\alpha]_D^{25}$ +6.0 (c=0.82, $CHCl_3$). υ_{max} / cm^{-1} 1649. δ_H (400 MHz, $CDCl_3$) 2.74 (1H, dd, J = 9.0, 13.7 Hz, PhCHH'), 3.27 (1H, dd, J = 4.9, 13.7 Hz, PhCHH'), 4.14 (dd, 1H, J = 7.3, 8.5 Hz, CHH'-O), 4.32 (dd, 1H, J = 8.6, 9.4 Hz, CHH'-O), 4.62 (m, 1H, CHN), 7.11-7.87 (m, 9H, ArH). δ_C (100 MHz, $CDCl_3$) 41.5 (CH_2Ph), 67.9 (CHN), 71.2 (CH_2O), 116.4 (ArC), 116.6 (ArC), 123.7 (ArC), 123.8 (ArC), 126.3 (ArC), 128.4 (ArC), 129.1 (ArC), 130.9 (ArC), 132.6 (ArC), 132.7 (ArC), 137.6 (ArC), 162.4 (C=N).

(4S)-2-(2-fluorophenyl)-4-isopropyl-1,3-oxazoline (9c). (46%) as a colourless oil. (found M^+, 207.1059. $C_{12}H_{14}FNO$ requires M^+, 207.1058). $[\alpha]_D^{25}$ -62 (c=0.5, $CHCl_3$). υ_{max} / cm^{-1} 1651. δ_H (400 MHz, $CDCl_3$) 0.91 (d, 3H, J=6.8 Hz, $CHCH_3$), 1.01 (d, 3H, J=6.8 Hz, $CHCH_3$), 1.89 (m, 1H, $CH(CH_3)_2$), 4.14 (m, 2H, CH_2O), 4.38 (m, 1H, CHN), 7.09-7.88 (m, 4H, ArCH). δ_C (100 MHz, $CDCl_3$) 16.6 (CH_3), 17.4 (CH_3), 31.0 ($CH(CH_3)_2$), 69.0 (CHN), 71.3 (CH_2O), 116.3 (ArC), 116.6 (ArC), 123.7 (ArC), 131.0 (ArC), 132.0 (ArC), 163.0 (C=N)

(4S)-2-(2-fluorophenyl)-4-phenyl-1,3-oxazoline (9d). (49%) as a colourless oil. (found M^+, 241.0903. $C_{15}H_{12}FNO$ requires M^+, 241.0903). $[\alpha]_D^{25}$ -30 (c=0.5, $CHCl_3$). υ_{max} / cm^{-1} 1647. δ_H (250 MHz, $CDCl_3$) 4.27 (1H, t J=8.4 Hz, CHN), 4.35 (1H, t, J=8.4Hz, CHH'-O), 4.79 (t, 1H, J=8.2Hz, CHHO), 7.13-8.00 (m, 4H, ArH). δ_C (63 MHz, $CDCl_3$) 70.0 (CHN), 74.5 (CH_2O), 123.9 (ArCH), 124.0 (ArCH), 124.7 (ArCH), 124.8 (ArCH), 126.6 (ArCH), 127.6 (ArCH), 128.5 (ArCH), 128.7 (ArCH), 131.3 (ArCH), 132.0 (ArCH), 133.0 (ArCH), 133.2 (ArCH), 133.5 (ArC), 142.0 (ArCH), 163.3 (C=N).

(4S)-4-^{t}butyl-2-(2-fluorophenyl)-1,3-oxazoline (9e). (56%) as a colourless oil. (found M^+, 221.1213. $C_{13}H_{16}FNO$ requires M^+, 221.1216). $[\alpha]_D^{25}$ -69.3 (c=1, $CHCl_3$). υ_{max} / cm^{-1} 1651. δ_H (400 MHz, $CDCl_3$) 0.95 (9H, s, $C(CH_3)_3$), 4.06 (1H, dd, J=7.7, 10.1 Hz, CHH'-O), 4.22 (t, 1H, J=7.7 Hz, CHN), 4.33 (1H, dd, J = 8.6, 10.1 Hz, CHH'-O), 7.14-7.86 (4H, m, ArH). δ_C (100 MHz, $CDCl_3$) 25.6 ($C(CH_3)_3$), 33.8 ($C(CH_3)_3$), 68.3 (CHN), 76.0 (CH_2O), 116.3 (ArC), 116.5 (ArC), 123.6 (ArC), 131.0 (ArC), 132.4 (ArC), 132.5 (ArC), 162.9 (C=N).

*General procedure preparation of (4S)-2-(2-diphenylphosphinophenyl)-4-substituted-1,3-oxazolines **10a-e**.*

Reaction is performed under an inert atmosphere. To a flame dried 50ml two-necked flask, is added potassium diphenylphosphide (1mmol) (as a 0.5M solution in THF) via syringe. The solution is then heated to reflux and the (4S)-4-substituted-2-(2-fluorophenyl)-1,3-oxazoline **9a-e** (1mmol) added as a solution in THF (2ml). The mixture is then stirred under reflux for 2 hours, whereupon the red solution of the phosphide fades to a pale yellow. The mixture is then transferred *via* cannula into a separating funnel and partioned between dichloromethane (20ml) and water (20ml). The dichloromethane layer is taken, dried over magnesium sulphate then the solvent removed *in vacuo*. The residue is purified by flash chromatography (light petroleum/ether 3:1) to afford a clean product.

(4S)-2-(2-diphenylphosphinophenyl)-4-methyl-1,3-oxazoline (10a). (80%) as a colourless solid. M.p. 93 - 95°C . (found M^+, 345.1303. $C_{22}H_{20}NOP$ requires M^+, 345.1282). $[\alpha]_D^{25}$ -7.5 (c=2.0, $CHCl_3$). υ_{max} / cm^{-1} 1650. δ_H (400 MHz, $CDCl_3$) 0.95 (3H, d, J = 6.5Hz, CH_3), 3.54 (1H, t, J = 7.6Hz), 4.08 - 4.21 (2H, m, CH_2O), 6.84 (1H, m, ArH), 7.20 - 7.70 (12H, m, ArH), 7.90 (1H, m, ArH) . δ_C (100 MHz, $CDCl_3$) 20.6 (CH_3), 61.7 (CHN), 73.4 (CH_2O), 127.7 (ArC), 128.1 (ArC), 128.2 (ArC), 128.3 (ArC), 128.5 (ArC), 128.6 (ArC), 128.8 (ArC), 130.2 (ArC), 130.4 (ArC), 130.6 (ArC), 132.3 (ArC), 133.2 (ArC), 133.6 (ArC), 133.8 (ArC), 133.9 (ArC), 134.0 (ArC), 134.3 (ArC), 163.3 (C=N).

(4S)-4-benzyl-2-(2-diphenylphosphinophenyl)-1,3-oxazoline (10b). (76%) as a colourless solid. M.p. 106 -108°C . (found M^+, 421.1573. $C_{28}H_{24}NOP$ requires M^+, 421.1595). $[\alpha]_D^{25}$ 14.0 (c=0.5, $CHCl_3$). υ_{max} / cm^{-1} 1649. δ_H (400 MHz, $CDCl_3$) 2.12 (1H, dd, J=9.1, 13.8Hz, CHH'Ph), 2.92 (1H, dd, J=5.1, 13.8Hz, CHH'Ph), 3.75 (1H, t, J=7.9Hz, CHH'), 4.01 (1H, t, J=8.8Hz, CHH'), 4.33 (1H, m, CHN), 6.86 - 7.07 (1H, m, ArH), 7.17 - 7.34 (17H, m, ArH), 7.85 - 7.88 (1H, m, ArH). δ_C (100 MHz, $CDCl_3$) 41.0 (CH_2Ph), 67.8 (CHN), 71.3 (CH_2O) 126.3 -138.1 (ArC), 163.8 (C=N).

(4S)-2-(2-diphenylphosphinophenyl)-4-isopropyl-1,3-oxazoline (10c). (76%) as a colourless solid. M.p. 84 - 86°C . (found M^+, 373.1597. $C_{24}H_{24}NOP$ requires M^+, 373.1595). $[\alpha]_D^{25}$ -40 (c=0.5, $CHCl_3$). υ_{max} / cm^{-1} 1651. δ_H (400 MHz, $CDCl_3$) 0.69 (3H, d, J = 6.7Hz, CH_3), 0.80 (3H, d, J = 6.7Hz, CH_3), 1.52 (1H, m, $CH(CH_3)_2$), 3.80 (2H, m, CHN and CH_2O), 4.10 (1H, m, CHN), 6.89 (1H, m, ArH), 7.20-7.70 (12H, m, ArH), 7.92 (1H, m, ArH). δ_C (100 MHz, $CDCl_3$) 18.2 (CH_3), 18.7 (CH_3), 32.7 ($CH(CH_3)_2$), 69.7 (CH_2O), 72.9(CHN),.127.9 - 138.1 (ArC) 162.9 (C=N)

(4S)-2-(2-diphenylphosphinophenyl)-4-phenyl-1,3-oxazoline (10d). (84%) as a colourless solid. M.p. 57 - 58 °C . (found M^+, 407.1413. $C_{27}H_{22}NOP$ requires M^+, 407.1439). $[\alpha]_D^{25}$ +24 (c=0.25, $CHCl_3$). υ_{max} / cm^{-1} 1649. δ_H (400 MHz, $CDCl_3$) 3.92 (1H, t, J = 8.4Hz, CHH'O), 4.55 (1H, dd, J = 8.3, 10.2Hz, CHH'O), 5.22 (1H, t, J = 9.5Hz, CHN), 6.89-8.01 (19H, m, ArH). δ_C (100 MHz, $CDCl_3$) 70.0 (CHN), 74.2 (CH_2O), 126.5-134.3 (ArCH), 137.7 (ArC), 141.9 (ArC). *m/z* (EI) 407, 302, 240.

(4S)-4-^{t}butyl-2-(2-diphenylphosphinophenyl)-1,3-oxazoline (10e). (92%) as a colourless solid. M.p. 114-116 °C . (found M^+, 387.1741. $C_{25}H_{26}NOP$ requires M^+, 387.1751). $[\alpha]_D^{25}$ -55.2 (c=0.6, $CHCl_3$). υ_{max} / cm^{-1} 1650. δ_H (400 MHz, $CDCl_3$) 0.72 (9H, s, $C(CH_3)_3$), 3.99 (1H, t, J = 8.3Hz, CHN or CH_2O), 4.10 - 4.21 (2H, m, CHN and/or CH_2O), 6.90 (1H, m, ArH), 7.20 - 7.80 (12H, ArH), 7.94 (1H, m, ArH). δ_C (100 MHz, $CDCl_3$) 25.7 ($C(CH_3)_3$), 33.4 ($C(CH_3)_3$), 68.1 (CHN), 75.8 (CH_2O), 127.9 (ArC), 128.0 (ArC), 128.1 (ArC), 128.2 (ArC), 128.3 (ArC), 128.4 (ArC), 129.7 (ArC), 130.2 (ArC), 130.6 (ArC), 131.1 (ArC), 131.6 (ArC), 131.7 (ArC), 133.3 (ArC), 133.5 (ArC), 134.0 (ArC), 134.2 (ArC), 138.5 (ArC).

Alternative Preparation of (4S)-2-(2-diphenylphosphinophenyl)-4-isopropyl-1,3-oxazoline (10c)

(4S)-2-(*o*-hydroxyphenyl)-4-isopropyl-1,3-oxazoline **12c** was prepared from *o*-cyanophenol **27** according to the literature procedure in 54% yield.[9] Trifluoromethanesulfonic anhydride (170ml, 1.04mmol) in dichloromethane (1 ml) was cooled to 0 °C before the dropwise addition of a solution of **12c** (210mg, 1.0mmol) and pyridine (92mg, 1.2mmol) in dichloromethane (3ml). Stirring was continued at 0°C for a further 2 hours. The mixture was diluted with water (10ml), extracted with dichloromethane (3 x 10ml), and the combined organic extracts dried ($MgSO_4$) and concentrated to yield a colourless oil (202mg, 0.6mmol, 60%). The product was used without purification. υ_{max}/cm^{-1} 1156 (SO_2O) ; δ_H 0.95 (3H, d, 7.0Hz Hz, CH_3), 1.08 (3H, d, 7.0 Hz, CH_3), 1.92-2.03 (1H, m, $CH(CH_3)_2$), 4.12-4.21 (2H, m, CH_2O),4.41-4.49 (1H, m, CHN), 7.28-8.15 (4H, m, ArH).

Crude triflate (115mg, 0.34mmol) in THF (1ml) was added dropwise to refluxing potassium diphenylphosphide (0.5M solution in THF, 1.0ml, 0.5mmol). The reaction was maintained at reflux for a further 14h. The mixture was diluted with diethyl ether (5ml) and washed with water (10ml). The separated organic layer was dried (K_2CO_3) and concentrated to a yellow oil (107mg, 0.29mmol, 84%). Analysis of the ^1H nmr of this material, and comparison with an authentic sample confirmed the presence of **10c** contaminated with minor impurites (<10%).

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