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Simple phosphinite–oxazoline ligands for asymmetric catalysis

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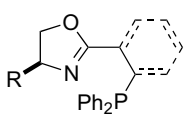
Abstract—4-(Hydroxymethyl)oxazolines, derived from (*S*)-serine methyl ester and a variety of acid chlorides (RCOCl), were reacted with Ph_2PCl to give new phosphinite–oxazoline P–N ligands. These mediate the palladium catalysed asymmetric alkylation with dimethyl malonate with the following racemic propenyl substrates $R^1CH{=}CHCH(OX)R^1$: (a) $R^1 = Ph$, $X = Ac$—96% e.e.(*S*) with $R = Ph$; (b) $R^1 = Me$, $X = CO_2{}^tBu$—70% e.e.(*S*) with $R = (\eta^5\text{-}C_5H_4)(\eta^4\text{-}C_4Ph_4)Co$. © 2001 Published by Elsevier Science Ltd.

Phosphorus–nitrogen donor oxazoline ligands have proven effective in numerous metal catalysed asymmetric methodologies.[1] In **1**, the first and most widely studied of these, the phosphorus centre is attached to an oxazoline 2-aryl,[2] 2-ferrocenyl[3] or 2-alkyl[4] substituent to provide a six-membered chelate on metal coordination. The alternative arrangement **2** with phosphorus attached to the oxazoline 4-substituent was recently reported,[5] these ligands permitting greater diversity of structure as the variable R need not be confined to an α-amino acid substituent. Such flexibility aids the rapid identification of the optimum ligand for a given substrate.

Structurally related to **2** are the phosphinite–oxazoline ligands **3** derived from D-glucosamine.[6] For the only pair of these ligands that may be directly compared, the outcome of palladium catalysed allylic substitution of 1,3-diphenylpropenyl acetate **9** with dimethyl malonate is very similar, the products from **2** (R = Ph) and **3** (R = Ph) having an 98% e.e. of *R* configuration and an 94% e.e. of *S* configuration respectively. As this change in product configuration is clearly related to the configuration at the oxazoline 4-position, we chose to investigate whether simple phosphinite–oxazoline ligands **4** might prove effective in this reaction. Our preliminary results are reported in this Letter.

We have previously utilised 4-(hydroxymethyl)-oxazolines **8a** and **8b** in conjunction with diethyl zinc for the synthesis of (*R*)-1-phenylpropanol from benzaldehyde.[7] Additional derivatives **8c–e** were similarly synthesised from (*S*)-serine methyl ester **5** by reaction with the appropriate acid chloride, followed by DAST mediated cyclisation of the resulting amide,[8] and subsequent ester reduction (Scheme 1). The enantiomeric excess of **8e** was determined as >95% by ^1H NMR analysis of the two esters derived from (*S*)- and (*R*)-Mosher's acid chloride.

Phosphinites **4a–e** were then prepared by DMAP mediated addition of chlorodiphenylphosphine followed by filtration through a plug of Al_2O_3 to remove the catalyst and triethylamine hydrochloride.[9] The utility of this ligand set was first tested in the aforementioned allylic alkylation reaction (Scheme 2). Having confirmed the superiority of CH_2Cl_2 over THF as a solvent for this reaction (Table 1, entry 2 versus 1), the five ligands were found to give selectivities related to the size of their R substituent, the best results being obtained with ligands containing the relatively small ferrocenyl (entry 4) or phenyl (entry 6) groups. Use of **4e** at 0°C (entry 7) gave a selectivity very similar to those described for **2** (R = Ph) and **3** (R = Ph), which were also obtained at this temperature. This result reveals that (a) changing from an alkyldiaryl phosphine (i.e. **2**) to a structurally similar diarylphosphinite does not change the selectivity or sense of asymmetric induction, and (b) the conformationally locked nature of phosphinite **3** is not necessarily required for high selectivities.



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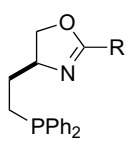

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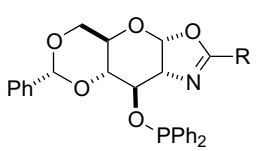

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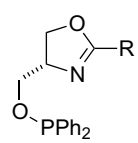

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* Corresponding author.

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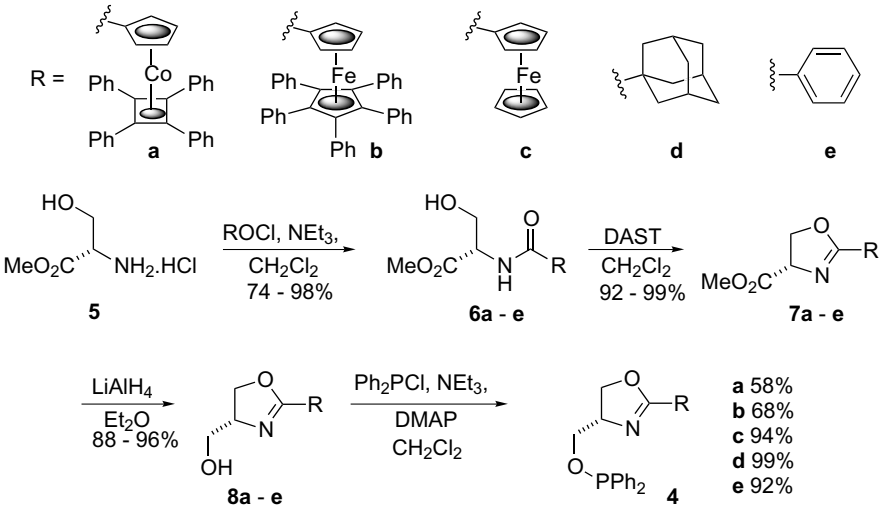
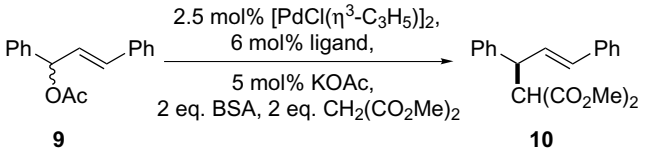
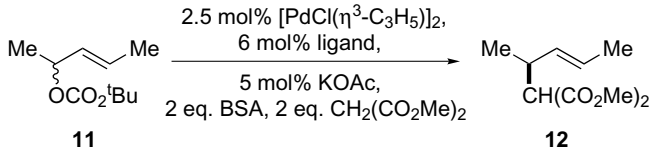


Scheme 1.



Scheme 2.



Scheme 3.

Table 1. Pd-catalysed conversion of **9** into **10** mediated by ligands **4a**–**e**[a]

Entry	Ligand	Solvent	Temperature (°C)	e.e. of **10** (Config.)[b]
1	**4a**	THF	20	53% (*S*)
2	**4a**	CH_2Cl_2	20	80% (*S*)
3	**4b**	CH_2Cl_2	20	52% (*S*)
4	**4c**	CH_2Cl_2	20	90% (*S*)
5	**4d**	CH_2Cl_2	20	67% (*S*)
6	**4e**	CH_2Cl_2	20	90% (*S*)
7	**4e**	CH_2Cl_2	0	96% (*S*)

[a] Reactions had proceeded to >95% conversion after 24 h.
[b] Determined by HPLC with a Diacel Chiralcel OD column (99:1 hexanes:propan-2-ol. Absolute configuration determined by comparison to (*S*)-**10** obtained with (*S*)-2-[(*S*)-2-(diphenylphosphino)ferrocenyl]-4-(1-methylethyl)oxazoline (94% e.e.).[3c]

We next examined the smaller and more demanding substrate **11** with the same ligand set (Scheme 3). Again CH_2Cl_2 proved superior to THF (Table 2, entry 2 versus 1), and the 85:15 selectivity obtained with **4a** is noteworthy due to the poorer selectivities reported with most P–N ligands in this reaction.[10] Either increasing (entry 3) or decreasing (entry 4) the size of the metallocene results in elimination or reduction of the enantioselectivity respectively, the other ligands also proving less successful (entries 5 and 6).

Table 2. Pd-catalysed conversion of **11** into **12** mediated by ligands **4a**–**e**[a]

Entry	Ligand	Solvent	Temperature (°C)	e.e. of **12** (Config.)[b]
1	**4a**	THF	20	30% (*S*)
2	**4a**	CH_2Cl_2	20	70% (*S*)
3	**4b**	CH_2Cl_2	20	0% –
4	**4c**	CH_2Cl_2	20	50% (*S*)
5	**4d**	CH_2Cl_2	20	11% (*S*)
6	**4e**	CH_2Cl_2	20	43% (*S*)

[a] Reactions had proceeded to >95% conversion after 48 h.
[b] Determined by GC with a Chrompack CP-Chirasil-DEX CB column. Absolute configuration determined by comparison to (*S*)-**12** derived with (*S*)-2-[(*S*)-2-(diphenylphosphino)ferrocenyl]-4-(1-methylethyl)oxazoline (12% e.e.).[3d]

In conclusion, easily synthesised phosphinite–oxazoline ligands **4** are simple alternatives to related phosphine and sugar derived phosphinite ligands **2** and **3**. Given the synthetic potential of ester intermediates **7**,[7] it is anticipated that these will provide the basis for ligand libraries applicable to a range of metal-catalysed asymmetric transformations.

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Spectrometry Service Centre, University of Wales, Swansea.

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9. Compound **4a**: δ_H ($CDCl_3$) 3.41 (2H, t, *J* 9.0, 2×CH*H*O), 3.70–3.76 (1H, m, CH*H*O), 3.80–3.99 (2H, m, CH*H*O and C*H*N), 4.65 (1H, brs, Cp), 4.72 (1H, brs, Cp), 4.96 (1H, brs, Cp), 5.08 (1H, brs, Cp), 7.01–7.41 (30H, m, Ph); δ_P {^{1}H} 115.7 (O*P*Ph_2).
   Compound **4b**: δ_H ($CDCl_3$) 3.11 (1H, q, *J* 8.9, CH*H*O), 3.69–3.78 (1H, m, CH*H*O), 3.82 (1H, t, *J* 8.9, C*H*HO), 3.89–4.07 (2H, m, C*H*HO and C*H*N), 4.28 (2H, s, Cp), 4.63 (1H, s, Cp), 4.66 (1H, s, Cp), 6.87–7.09 (25H, m, Ph), 7.12–7.29 (6H, m, Ph), 7.30–7.39 (4H, m, Ph); δ_P {^{1}H} 115.5 (O*P*Ph_2).
   Compound **4c**: δ_H ($CDCl_3$) 3.77–3.82 (1H, m, CH*H*O), 3.95–4.00 (1H, m, CH*H*O), 4.06 (5H, s, Cp), 4.22–4.34 (3H, m, CH_2O and C*H*N), 4.24 (2H, s, Cp), 4.64 (2H, s, Cp), 7.20–7.30 (6H, m, Ph), 7.37–7.43 (4H, m, Ph); δ_P {^{1}H} 115.3 (O*P*Ph_2).
   Compound **4d**: δ_H ($CDCl_3$) 1.59 (6H, brs, 3×CH_2), 1.78 (6H, brs, 3×CH_2), 1.97 (3H, brs, 3×C*H*), 3.76–3.80 (1H, m, CH*H*O), 3.86–4.25 (4H, m, 3×CH*H*O+C*H*N), 7.21–7.33 (4H, m, Ph), 7.34–7.50 (4H, m, Ph), 7.61–7.78 (2H, m, Ph); δ_P {^{1}H} 115.0 (O*P*Ph_2).
   Compound **4e**: δ_H ($CDCl_3$) 3.87–3.93 (1H, m, -CH*H*O-), 4.04–4.06 (1H, m, -C*H*HO-), 4.36 (2H, dd, *J* 7.9 3.1, -CH_2O-), 4.43–4.51 (1H, m, -C*H*N-), 7.15–7.42 (13H, m, Ph), 7.82–7.84 (2H, m, Ph); δ_P {^{1}H} ($CDCl_3$) 116.4 (-O*P*Ph_2).
10. For notable exceptions, see: (a) Trost, B. M.; Krueger, A. C.; Bunt, R. C.; Zambrano, J. *J. Am. Chem. Soc.* **1996**, *118*, 6520; (b) Wiese, B.; Helmchen, G. *Tetrahedron Lett.* **1998**, *39*, 5727.