



# Planar chiral mimetics. A new approach to ligand design for asymmetric catalysis

Geraint Jones, David C. D. Butler and Christopher J. Richards\*

Department of Chemistry, Cardiff University, PO Box 912, Cardiff CF10 3TB, UK

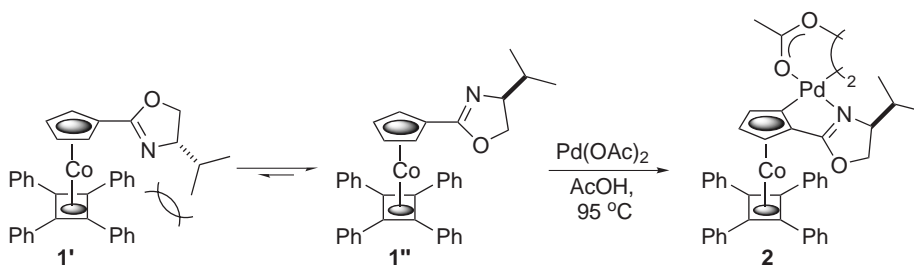
Received 31 August 2000; accepted 3 October 2000

## Abstract

(*S*)-Serine methyl ester is readily transformed into 4-(hydroxymethyl)oxazoline ligands containing either a 2-( $\eta^5$ -cyclopentadienyl)( $\eta^4$ -tetraphenylcyclobutadiene)cobalt or a 2-(1,2,3,4,5-pentaphenyl)-ferrocene substituent. The influence of the bulky metallocenes result in these ligands mimicking planar chirality, as demonstrated by their catalysis of the addition of diethylzinc to benzaldehyde resulting in (*R*)-1-phenylpropanol (75% e.e.). © 2000 Published by Elsevier Science Ltd.

**Keywords:** asymmetry; catalysts; metallocenes; oxazolines.

Planar chiral organometallics, and especially metallocenes such as ferrocene, have been extensively utilised as the basis of a wide variety of chiral ligands for application in asymmetric synthesis.<sup>1</sup> As part of a programme investigating the synthesis of new planar chiral complexes, we recently reported that the metallocene appended oxazoline **1** undergoes highly diastereoselective metallation when heated with palladium acetate to give exclusively palladacycle **2** (Scheme 1).<sup>2</sup> The outcome of this reaction was rationalised by the destabilisation of conjugated rotamer **1'** over the alternative **1''** due to an unfavourable interaction in the former between the oxazoline isopropyl substituent and the tetraphenyl floor of the metallocene.

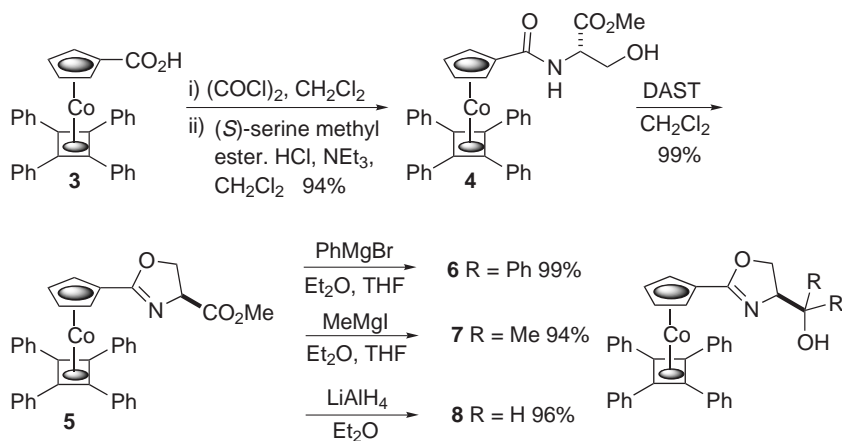


Scheme 1.

\* Corresponding author.

As a consequence of this bulky moiety, the oxazoline group of **1** may be regarded as being in an environment of virtual planar chirality, i.e. as if the heterocycle were covalently bound to a second position of the cyclopentadienyl ring, as is actually the case in complex **2**. This example of a chiral relay offers the potential to synthesise simple alternatives to planar chiral ligands that require only a single element of central chirality. In this Letter we report on our initial efforts towards this goal with the generation of functionalised oxazolines that act as catalysts for the addition of diethylzinc to benzaldehyde.

Starting from the readily available carboxylic acid **3**,<sup>2</sup> amide **4** was readily obtained via reaction of the intermediate acid chloride with (*S*)-serine methyl ester hydrochloride in the presence of triethylamine. Dehydrative ring-closure was achieved with DAST<sup>3</sup> to give oxazoline **5** in 93% overall yield (Scheme 2). From this three new ligands **6–8** were readily generated with each containing a  $\beta$ -hydroxyl group relative to the oxazoline nitrogen,<sup>4</sup> an arrangement essentially identical to the  $\beta$ -hydroxy amines that have been extensively used in conjunction with dialkylzinc reagents.<sup>5</sup>



Scheme 2.

Addition of 1.5 equivalents of diethylzinc to benzaldehyde **9** in the presence of 5 mol% of these ligands resulted in the clean formation of **10**, the highest selectivity of (*R*) to (*S*) enantiomers being obtained with the parent hydroxymethylene complex **8** (Table 1, entry 3). In contrast, phenyl and methyl substituents adjacent to the hydroxyl group in **6** and **7** result in an erosion of selectivity correlated to the size of these alternatives to hydrogen (entries 1 and 2)<sup>6</sup> (Scheme 3).

Table 1  
Addition of diethylzinc to benzaldehyde<sup>a</sup>

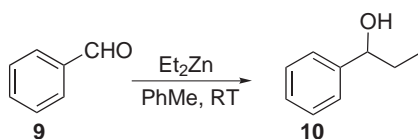
Entry	Catalyst <sup>b</sup>	e.e. of <b>10</b> <sup>c</sup> (config.) <sup>d</sup>
1	<b>6</b>	8 ( <i>R</i> )
2	<b>7</b>	54 ( <i>R</i> )
3	<b>8</b>	68 ( <i>R</i> )
4	<b>14</b>	75 ( <i>R</i> )

<sup>a</sup> **9** (1.0 mmol), toluene (5 ml), Et<sub>2</sub>Zn (1 M in hexanes, 1.5 ml), all reactions gave >90% conversion after 24 h.

<sup>b</sup> 5 mol%.

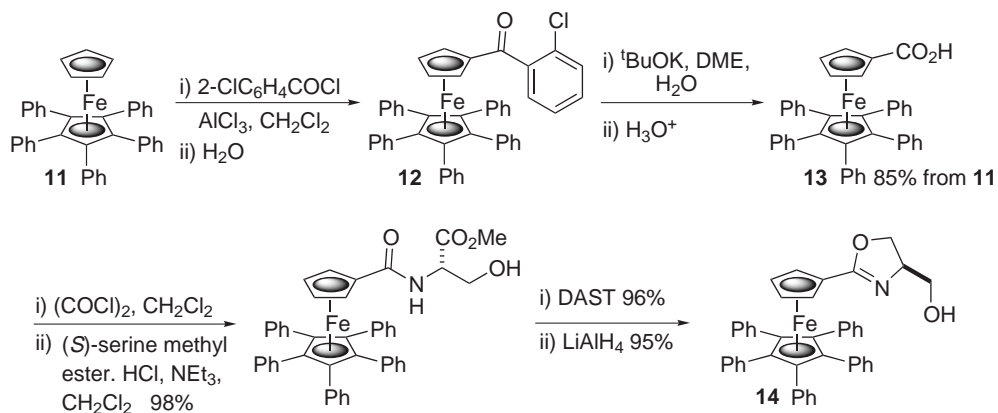
<sup>c</sup> Determined by GC.

<sup>d</sup> Determined by GC comparison to commercial (*R*)-1-phenylpropanol.



Scheme 3.

Thus we reasoned that an increase in selectivity might alternatively relate to the size of the floor as defined by the metallocene phenyl substituents. To increase the number of these from four to five required a switch to the chemistry of pentaphenylferrocene **11**. Although first reported in 1965 by Pauson<sup>7</sup> we were surprisingly unable to find any reports on the direct functionalisation of this complex.<sup>8</sup> This however proved to be straight forward as reaction with 2-chlorobenzoyl chloride and aluminium chloride, as previously described for ferrocene itself,<sup>9</sup> cleanly gave aryl ketone **12** (Scheme 4). This in turn was hydrolysed to give pentaphenylferrocene carboxylic acid **13** in 85% overall yield. Use of this as a starting material for the same chemistry as described above cleanly gave the novel oxazoline complex **14** in excellent yield.

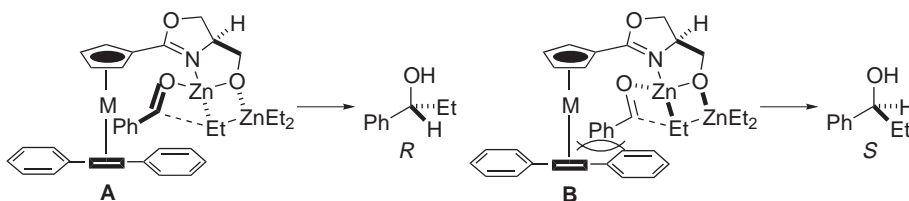


Scheme 4.

Application of **14** to the diethylzinc/benzaldehyde reaction as before led to an increase in selectivity for the (*R*)-enantiomer (Table 1, entry 4). Increasing the hexane component of the solvent mixture to 50% and decreasing the reaction temperature to 0°C made no appreciable difference to the enantioselectivity.

The absolute configuration of the 1-phenylpropanol resulting from these reactions may be rationalised by considering the two alternative reaction pathways **A** and **B**. Orientation of the oxazoline 4-substituent away from the floor defined by the phenyl groups results in a preference for the oxazoline–metallocene rotamer drawn in both **A** and **B**. Following coordination to zinc, the ethyl group to be transferred may be aligned either away (**A**) or towards (**B**) the alkoxymethylene arm of the oxazoline. In the former, coordination of benzaldehyde from the side opposite to the floor results in ethyl transfer to the *Re* face and formation of the major *R*-enantiomer. In the alternative **B** the coordinated benzaldehyde is in close proximity to the bulky floor unless the oxazoline rotates into an alternative conformation. This may occur to a greater extent when methyl and phenyl groups are adjacent to the zinc coordinated alkoxide,

with these substituents favouring alignment of the transferable ethyl group towards the alkoxyethylene arm. Clearly too much bulk is detrimental to selectivity with this system. However, for complexes **8** and **14**, the ability of the phenyl floor to cover one face of the heterocycle enables the comparison with planar chirality to be made. This arrangement is equivalent to the oxazoline itself being  $\pi$ -bonded to a metal/ligand fragment.<sup>10</sup>



In conclusion, we have demonstrated that functionalised oxazoline ligands attached to either a tetraphenyl/cobalt or a pentaphenyl/iron derived metallocene are readily synthesised in excellent yield. The presence of the multiple phenyl groups results in a ligand/metal environment equivalent to that displayed by planar chiral organometallics. The use of related mimetics in reactions of wider applicability is currently under investigation.

## Acknowledgements

We wish to thank the EPSRC for financial support (GR/M55893) and also Rob Jenkins for his assistance with this work.

## References

- For recent reviews, see: (a) Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377. (b) Kagan, H. B.; Riant, O. *Advances in Asymmetric Synthesis*; Hassner, A., Ed.; JAI Press: Greenwich, CT, 1997; Vol. 2, pp. 189–235.
- Stevens, A. M.; Richards, C. J. *Organometallics* **1999**, *18*, 1346.
- Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165.
- The use of related 2-alkyl and 2-aryl oxazolines as ligands for the addition of diethylzinc to aldehydes was recently reported: Imai, Y.; Matsuo, S.; Zhang, W.; Nakatsuji, Y.; Ikeda, I. *Synlett* **2000**, 239.
- Review: (a) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. See also: (b) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028.
- For comparison, (*S*)-2-methyl-4-(2-(2-hydroxy)propyl)oxazoline led to the formation of (*S*)-**10** in 7% e.e., see reference 4.
- McVey, S.; Pauson, P. L. *J. Chem. Soc.* **1965**, 4312.
- Functionalised heteroleptic pentaphenylferrocene derivatives have been directly synthesised from cyclopentadiene precursors: Hodous, B. L.; Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 2637.
- Reeves, P. C. *Org. Synth.* **1977**, *56*, 28.
- Planar chiral ligands have been extensively applied to the reaction between dialkylzinc reagents and aldehydes, see reference 1a. However, the only direct comparison possible, with respect to environment and chelate size, is with (–)-2-(hydroxymethyl)azaferrocene (absolute configuration unknown). This led to the formation of (*S*)-**10** in 58% e.e.: Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444.