The importance of nitrogen substituents in chiral amino thiol ligands for the asymmetric addition of diethylzinc to aromatic aldehydes

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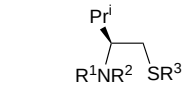
A new series of *N*,*S*-chelate ligands derived from (*S*)-valine, which possess the capability of a stereogenic nitrogen donor atom, are catalysts for the addition of diethylzinc to aromatic aldehydes and gave the product secondary alcohols in up to 82% ee.

The successful use of metal complexes for enantioselective catalysis is largely dependant upon the structure and electronic properties of chiral ligands. We set out to develop a series of new chiral *N*,*S*-chelates, derived from amino acids, that would help us understand the origins of chirality in a variety of asymmetric catalytic processes. Very recently enantiomerically pure amino thiols have been shown to catalyse the addition of diethylzinc to benzaldehyde in high enantiomeric excess. Most noteworthy are systems derived from ephedrine,[1,2] (1*R*, 2*S*)-(−)-1,2-diphenyl-2-aminoethanol[3] and van Koten's *N*,*S*-chelated bis{2-[(*R*)-1-)dimethylamino)ethyl]phenylthiolato}-zinc complex.[4] All of these ligands possess a symmetrical nitrogen donor atom and we anticipated that a potentially stereogenic nitrogen donor atom could have positive effects in this reaction system and other metal catalysed processes. In the design of our ligands careful attention was paid to the notion that the chirality inherent to the backbone of the amino acid could be transmitted closer towards the reaction centre by the correct choice of substituents on nitrogen. Upon chelation, the nitrogen atom could become stereogenic and reinforce the stereoinducing power of the ligand. We have tackled this idea by preparing ligands **1**–**5** that all possess a ligating sulfur atom in place of the hydroxy group from the derived amino acid. We hoped we could get good catalytic activity as sulfur would have a high affinity towards most metals useful in catalytic reactions, and has less tendency to diminish the Lewis acidity of the metal compared to metal alcoholates.‡ For instance, when ligand **1**



1 $R^1 = R^2 = Ph$, $R^3 = H$
2 $R^1 = R^2 = Bn$, $R^3 = H$
3 R^1–$R^2 = -(CH_2)_5-$, $R^3 = H$
4 $R^1 = Ph$, $R^2 = Me$, $R^3 = H$
5 $R^1 = R^3 = Ph$, $R^2 = H$

chelates to a metal atom the nitrogen donor with two phenyl substituents will possess different orientations of its atomatic rings [Fig. 1(*a*)]. The rotational freedom of the β-phenyl ring will be restricted by the proximity of the chiral centre. The

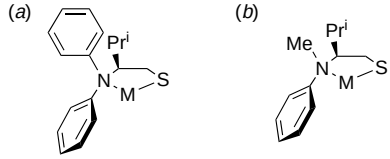
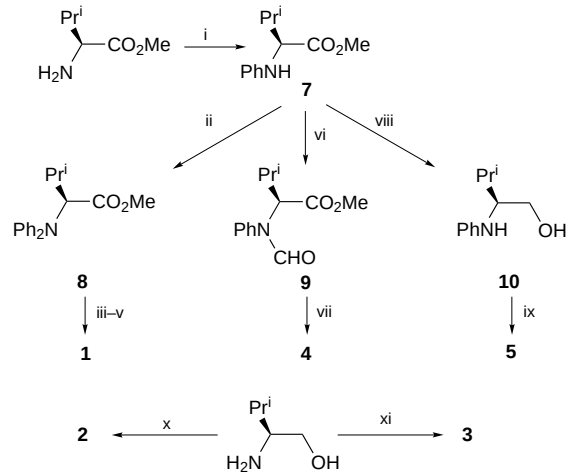


Fig. 1

orientation of this phenyl ring will affect that of the α-phenyl ring and render the nitrogen atom stereogenic.§ In ligands of type **4** the nitrogen atom is substituted with a large and small group. Upon coordination to a metal atom the *N*-methyl substituent should occupy the same face as the chiral centre on the backbone of the chelate, forcing the larger phenyl substituent to the underface [Fig. 1(*b*)], thus again rendering the nitrogen atom stereogenic.¶ Here we report our initial studies concerning these ligands in the 1,2-addition of diethylzinc to aromatic aldehydes, in order to assay their enantioselectivity and catalytic reactivity.

The syntheses of our desired ligands were accomplished in high yield starting from either (*S*)-valine methyl ester or (*S*)-valinol derived from the reduction of (*S*)-valine (Scheme 1).[5] Diphenylation of (*S*)-valine methyl ester or (*S*)-valine was not possible using palladium catalysed methods recently reported.[6] Instead monophenylation using triphenylbismuth diacetate, promoted or catalysed by copper diacetate,[7] gave **7** in 85% yield. This material could then be phenylated again, under similar conditions, to give **8** in 69% yield. Reduction of the diphenylamine **8** with LAH was followed by substitution of the hydroxy function with sulfur under Mitsunobu-type conditions and gave ligand **1** in 75% yield. Formation of the *N*-phenylformamide by warming **7** with acetic formic anhydride[8] in 96% yield was followed by treatment with LAH to effect simultaneous reduction to the *N*-methyl substituent and



Scheme 1 *Reagents and conditions*: i, $Ph_3Bi(OAc)_2$ (1.2 equiv.), $Cu(OAc)_2$ (10 mol%), CH_2Cl_2, room temp., 24 h, 85%; ii, $Ph_3Bi(OAc)_2$ (1.5 equiv.) $Cu(OAc)_2$ (1 equiv.), CH_2Cl_2, room temp., 14 d, 69%; iii, LAH (4 equiv.), Et_2O–THF, room temp., 1 h; iv, diisopropyl azodicarboxylate (2 equiv.), Ph_3P (2 equiv.), AcSH (2 equiv.), room temp., 77% over two steps; v, LAH (4 equiv.) Et_2O–THF, 0 °C, 5 min, 98%; vi, AcOCHO (2.6 equiv.) HCO_2H (3.2 equiv.), THF, 70 °C, 2.5 h, 96%; vii, LAH (5 equiv.) Et_2O, 60 °C, 0.5 h, then (iv) followed by (v), 84% over three steps; viii, LAH (2 equiv.), Et_2O–THF, room temp., 0.5 h, 93%; ix, PhSSPh (3 equiv.), Bu_3P (4 equiv.), THF, 80 °C, sealed tube, 24 h, 75%; x, BnBr (2.2 equiv.), K_2CO_3 (2.5 equiv.), EtOH, room temp. 24 h, 91%, then (iv) followed by (v), 81% over two steps; xi, $Br(CH_2)_5Br$ (2 equiv.), K_2CO_3 (5 equiv.), EtOH, 60 °C, 48 h, 78%, then (iv) followed by (v), 72% over two steps

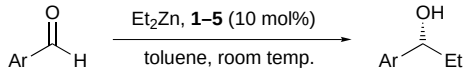
hydroxy function. Substitution by sulfur as before gave ligand **4** in 84% yield over three steps. Treatment of **7** with LAH gave alcohol **10** in 93% yield which was converted to the phenylthiol ligand **5** by heating in a sealed tube with diphenyl disulfide and tri-*n*-butylphosphine in 75% yield.[9]

Dibenzylation of (*S*)-valinol was achieved by treatment with benzyl bromide and potassium carbonate in 91% yield. Dialkylation of the amine function of (*S*)-valinol with 1,5-dibromopentane, under similar conditions, proceeded in 78% yield to form a piperidine. Substitution of the hydroxy function in each of these compounds by the aforementioned method gave ligands **2** and **3** in 81 and 72% yield, respectively (Scheme 1). The enantiohomogeneity of these ligands has been verified by racemic synthesis followed by NMR and HPLC comparison of their Mosher derivatives with the enantiomerically pure materials.

With these ligands in hand we screened their effectiveness as enantioselective catalysts in the addition of diethylzinc to aromatic aldehydes. Our initial experiments in this area are promising, as summarised in Table 1, and show good levels of enantioinduction in the presence of catalytic amounts (10 mol%) of the ligands **1**–**5**. Reactions were performed in toluene, at room temperature, for 3–20 h using 2.2 equiv. of diethylzinc.

These preliminary studies indicate that giving the nitrogen atom the potential to become stereogenic leads to a better system for enantioselection, as evidenced by the superior enantioselection of ligands **1** and **4** over **2** and **3** respectively. The best enantioselection (82% ee, entries 8 and 9) found with ligand **4** suggests that the donating ability of the nitrogen lone pair could be a factor in the efficiency of these ligands. This necessitates the need for further studies to try and separate the steric and electronic factors that are responsible for enhanced enantioselection. Ligands having a labile proton on nitrogen perform very poorly as catalysts in this particular reaction and along with the desired addition product, benzyl alcohol (38%) was formed from reduction of benzaldehyde.[10] These results show that non-symmetrical phenyl-substituted nitrogen donor atoms have a positive effect on the efficiency of these particular ligand systems. We believe we have a system with which we can probe the origins of chiral induction by further manipulation of the steric and electronic properties of these ligands. Further systematic modifications, studies designed to describe a transition state model and investigation of other metal catalysed systems will be reported in due course.

Table 1 Diethylzinc additions to aromatic aldehydes catalysed by chelate ligands **1**–**5**



Entry	Ligand	Ar	Yield (%)[a]	Ee (%)[b]
1	**1**	Ph	85	74
2	**1**	*o*-MeOC$_6$H$_4$	88	52
3	**1**	*p*-MeOC$_6$H$_4$	91	62
4	**2**	Ph	91	58
5	**3**	Ph	78	66
6	**3**	*o*-MeOC$_6$H$_4$	92	65
7	**3**	*p*-MeOC$_6$H$_4$	100	62
8	**4**	Ph	80	82
9	**4**	*o*-MeOC$_6$H$_4$	83	82
10	**4**	*p*-MeOC$_6$H$_4$	90	78
11	**5**	Ph	35[c]	0

[a] Isolated yield. [b] Determined by chiral GLC using a Chrompack™ CP-Cyclodex B column or optical rotation (see note ‖). [c] Reaction time 3 days.

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Notes and References

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‡ These original assumptions have been supported by other workers (ref. 11).

§ A similar transmission of chirality occurs in the successful chiral diphosphine ligand chiraphos in various asymmetric palladium catalysed reactions (ref. 12).

¶ A similar conformational analysis has been invoked to explain the excellent enantioselectivities obtained in Diels–Alder reactions using an enantiomerically pure [N,*N*′-bis(trifluoromethylsulfonyl)-1,2-diphenylethane-1,2-diamine]aluminium complex as catalyst (ref. 13).

‖ In each case a positive rotation was obtained, indicating the (*R*)-enantiomer (ref. 14).

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