

# A long-range chiral relay *via* tertiary amide group in asymmetric catalysis: new amino acid-derived N,P-ligands for copper-catalysed conjugate addition†

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New N,P-ligands **4–6**, derived from valinol and prolinol, respectively, have been developed for the asymmetric, copper(I)-catalysed conjugate addition of diethylzinc to unsaturated ketones; the tertiary amide group has been shown to effectively relay the chiral information from the ligand backbone to the active centre.

Development of methods for asymmetric synthesis has become one of the leading topics in the ongoing quest for new synthetic methodologies. A vast number of catalytic processes allowing conversion of prochiral substrates into chiral products of high enantiomeric purity have been reported.<sup>1</sup> Two complementary approaches to the catalyst design can be identified: (i) development of the structurally new chiral ligands and (ii) seeking enhancement of the enantioselectivity by modification of the known catalytic systems. In these efforts, exploitation of the chiral relay effect represents an emerging new strategy.<sup>2</sup>

The term “chiral relay” was introduced by Davies for the auxiliary-controlled enantioselective synthesis of chiral  $\alpha$ -amino acids.<sup>3</sup> Here, the conformationally flexible tertiary amide group placed in between the source of chirality and the reaction centre has been shown to effectively convey the chiral information which resulted in excellent diastereoselectivities. In this model the chiral centre constitutes an integral part of the molecule and hence serves as a stoichiometric chiral auxiliary.

An extension to catalytic processes has been reported by Sibi<sup>4</sup> and Renaud.<sup>5</sup> In their approach, a conformationally flexible non-chiral auxiliary is incorporated into the substrate to relay the chiral environment created by a chiral Lewis acid. In this case, the chiral information is conveyed from an external source, namely the chiral catalyst, generated from a metal precursor and a conventional chiral ligand.

Herein, we report on a different approach to the utilisation of the chiral relay effect. Our strategy is based on the integration of the chiral relay network into the ligand architecture. Morimoto<sup>6</sup> has recently applied N,P-ligands **3a,b** (Chart 1) to enantioselective copper-catalysed conjugate addition of diethylzinc to cyclohexenone **1a** (Scheme 1). With ligand **3a**, the product **2a** was obtained in 52% ee (toluene,  $-20\text{ }^{\circ}\text{C}$ ), while the 6-methylpyridine analogue **3b** gave lower enantioselectivity (40% ee). Assuming that the coordination to the metal occurs through the pyridine and phosphine groups, it would result in the formation of an eight-membered ring. The single chiral centre in this complex is rather distant from the metal to be able to effectively influence the new bond-forming process occurring at the metal. As a result, low enantioselectivity was attained. We reasoned that introduction of an additional alkyl group at the amide nitrogen should add more bias to the chelate by forcing the side-chain of the amino acid backbone and the *N*-alkyl group away from each other. In turn, the resulting arrangement should create an appropriate conformational twist about the carbonyl–pyridine bond, thereby creating a chiral

axis.<sup>7</sup> In this way, the chiral information from the amino acid backbone would be relayed to the metal.

To verify this hypothesis, the *N*-methyl amide **4a** was prepared and employed in the Cu-catalysed conjugate addition of diethylzinc to  $\alpha,\beta$ -unsaturated ketones (Scheme 1, Table 1).<sup>8</sup> While in the case of cyclohexenone **1a**, *N*-methylation did not affect the enantioselectivity, a noticeable increase (from 55% to 68% ee; entries 1 and 2) was detected for cycloheptenone **1b**. However, the most dramatic change in the stereochemical outcome was observed in the case of chalcone **1c** as a substrate. Here, the *N*-methylation of the ligand resulted in a substantial improvement of enantioselectivity (from 30 to 71% ee; entries 1 and 2) and led to the formation of the opposite enantiomer!

Another difference between the *N*-methylated ligand and its *N*-H analogue is that the enantioselectivity can be further improved by tuning the steric bulk of the pyridine moiety. Ligands **4b–d**, prepared from the corresponding 6-methylpicolinic, 6-phenylpicolinic and quinaldic acids, respectively, all showed an increase in enantioselectivity compared to **4a** (entries 3–5). The best results in this series were obtained with ligand **4b**, which gave up to 86% ee (entry 3).

The size of the *N*-alkyl group proved to be crucial, with methyl being optimal. The *N*-methyl was sufficient to induce the required conformational change but still small enough not to overcrowd the system. On the other hand, ligand **5** with an *N*-

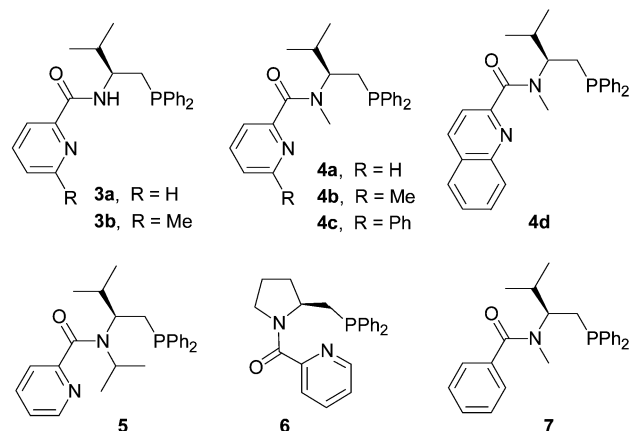
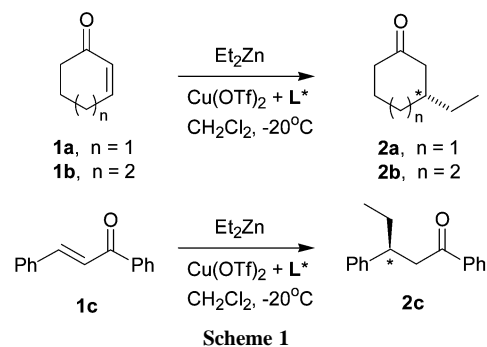


Chart 1 Chiral ligands.

† Electronic supplementary information (ESI) available: synthesis and characterisation of chiral ligands **4–7**; experimental details of catalytic Michael addition, characterisation of the products and enantioselectivity determination. See <http://www.rsc.org/suppdata/cc/b3/b304131j/>

**Table 1** The Cu-catalysed addition of diethylzinc to unsaturated ketones with ligands **3–7** (Scheme 1)<sup>a</sup>

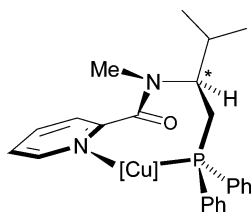
Entry	Ligand	Substrate					
		<b>1a</b>	<b>1b</b>	<b>1c</b>			
		Yield (%) <sup>b</sup>	Ee (%) <sup>c</sup>	Yield (%) <sup>b</sup>	Ee (%) <sup>c</sup>	Yield (%) <sup>b</sup>	Ee (%) <sup>c</sup>
1	<b>3a</b>	61	62 ( <i>S</i> )-(–)	77	55 (–)	82	30 ( <i>S</i> )-(–)
2	<b>4a</b>	84	60 ( <i>S</i> )-(–)	82	68 (–)	78	71 ( <i>R</i> )-(–)
3	<b>4b</b>	92	83 ( <i>S</i> )-(–)	90	86 (–)	86	81 ( <i>R</i> )-(–)
4	<b>4c</b>	86	81 ( <i>S</i> )-(–)	81	87 (–)	84	41 ( <i>R</i> )-(–)
5	<b>4d</b>	77	66 ( <i>S</i> )-(–)	75	80 (–)	78	78 ( <i>R</i> )-(–)
6	<b>5</b>	89	19 ( <i>R</i> )-(–)	90	23 (+)	52	3 ( <i>S</i> )-(–)
7	<b>6</b>	91	7 ( <i>S</i> )-(–)	76	7 (+)	90	29 ( <i>R</i> )-(–)
8	<b>4a<sup>d</sup></b>	—	—	—	—	13	8 ( <i>S</i> )-(–)
9	<b>7</b>	—	—	—	—	39	26 ( <i>S</i> )-(–)

<sup>a</sup> The reactions were carried out at 1.0 mmol scale with 1.1 equiv of Et<sub>2</sub>Zn in CH<sub>2</sub>Cl<sub>2</sub>, in the presence of the catalyst generated *in situ* from Cu(OTf)<sub>2</sub> (2 mol%) and the ligand (3 mol%), at –20 °C. <sup>b</sup> Isolated yield. <sup>c</sup> The enantioselectivity was determined by chiral GC or HPLC. The absolute configuration of the products was determined by comparison of their optical rotation and their GC and HPLC behaviour with the literature data and with the behaviour of the authentic samples (for details see ESI†). <sup>d</sup> The reaction was carried out in the absence of the Cu salt.

isopropyl group lost the enantioselectivity (Table 1, entry 6). The importance of the conformational twist introduced by the *N*-Me group about the bond linking it to the stereogenic centre can be illustrated with ligand **6**, based on proline, where such a twist cannot be achieved as the alkyl substituents are tied up in the cycle. The use of ligand **6** resulted in a dramatic decrease in enantioselectivity (Table 1, entry 7). A possible structure of the complex CuCl<sub>2</sub>·**4a**, as predicted by molecular modelling, is shown in Fig. 1.

A set of experiments was performed to provide a better insight into the structure of the active catalyst. Thus, in the absence of a copper salt, **1c** was converted into (*S*)-(+)-**2c** in a very low yield and poor enantioselectivity (13% and 8%, respectively; entry 8), confirming the crucial involvement of copper in the catalysis.† The role of the pyridine unit was investigated with the aid of ligand **7** lacking the pyridine nitrogen. Again, (*S*)-(+)-**2c** was formed in low yield and enantioselectivity (39% and 26%, respectively; entry 9).

In the <sup>1</sup>H NMR spectrum of a 1 : 1 complex of AgOTf and ligand **4a**, generated as a model system, the amide (*E/Z*)-isomers, present in the free ligand, collapsed into one. The signals of the pyridine protons were shifted compared to the free ligand and sharpened, which is consistent with the coordination to the metal. Broadening of the signals in the amino acid backbone suggests a certain degree of flexibility of the CH<sub>2</sub> group; by contrast, signals for the *N*-Me and *i*-Pr groups involved in the chiral relay remained sharp. In the <sup>31</sup>P NMR spectrum, free ligand exhibited two signals (at –22.1 and –24.2 ppm), while on coordination to AgOTf they coalesced into one (at –1.0 ppm). The IR spectrum showed no difference in the amide frequency of the free and coordinated ligand (1635 cm<sup>–1</sup>), indicating that the amide group was not involved in the coordination. Similar results were obtained with ligand **3a**, confirming that in both cases the bidentate coordination is realised and the favourable change of conformation in the eight-membered chelate CuCl<sub>2</sub>·**4a** is attributable to the tertiary amide group. A weak negative non-linear effect was observed in the catalytic reaction which implies either an aggregation of the active complex or formation of a dimeric species.

**Fig. 1** Proposed chelation in the Cu(II)–**4a** complex.

In conclusion, we have demonstrated that the tertiary amide group in new amino acid-based ligands **4a–d** can relay the chiral information to the metal coordinated. It controls the level and the sense of asymmetric induction in the Cu-catalysed conjugate addition of Et<sub>2</sub>Zn to enones with ≤87% ee. Extension of this principle is currently being pursued in this Laboratory.

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## Notes and references

† Note that Et<sub>2</sub>Zn is inert even to aldehydes and can be activated by a suitable ligand, which distorts its stable, rod-shape geometry.<sup>9</sup>

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