



## Scalemic $\beta$ -Amino Sulfide Ligands: Use in Enantioselective Conjugate Additions and X-Ray Analysis of a Dimeric Copper(I) Complex

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**Abstract:** The enantioselective conjugate addition using a number of scalemic  $\beta$ -amino sulfide ligands to achieve enantiomeric excesses of up to 64% are described together with the X-ray absolute structure analysis of a dimeric copper(I) complex. Copyright © 1996 Elsevier Science Ltd

The enantioselective conjugate addition of organocuprate reagents to  $\alpha,\beta$ -unsaturated substrates to afford scalemic  $\beta$ -substituted carbonyl compounds is a long standing problem that continues to be of considerable synthetic interest.<sup>1</sup> Although a number of methods have been reported to effect the enantioselective conjugate addition of organocuprates, the most popular procedures have involved the use of chiral heterocuprates where the stereodifferentiation results from a covalently bound, non-transferable chiral ligand or catalyst. In this context, the most notable have been the use of chiral O-heterocuprates,<sup>2</sup> N-heterocuprates<sup>3,4</sup> and the catalytic scalemic S-heterocuprates.<sup>5</sup> While these endeavours and many others represent significant advances in enantioselective conjugate additions, there still does not exist a general solution whereby high enantioselectivities can be achieved for a broad range of substrates and transferred groups. The transfer of a methyl group to five and six membered ring enones is particularly problematic giving at best moderate ees with organoheterocuprates (0-58% ee for 2-cyclohexen-1-one, 0-32% ee for 2-cyclopenten-1-one).<sup>1,3,4</sup> The original claims by Dieter and Tokles of high optical purities ( $\leq 81\%$ )<sup>4b</sup> for the transfer of a methyl group to 2-cyclohexen-1-one **1** using prolinol ethers were subsequently downsized (0-30%)<sup>4a</sup> as a consequence of variable results that were inconsistent with the earlier report. In the light of the problems with the enantioselective addition to six membered ring enones, several years ago we initiated a series of studies to address this issue. Based on the proposed mechanism of enantioselectivity for N-heterocuprates<sup>3,4b</sup> we anticipated that an alternative strategy would be to investigate enantiopure ligands that were capable of *bis* coordination to copper(I). Initial experiments with enantiopure biphosphines were disappointing for the addition of a methyl group to chalcone.<sup>6</sup> This led us to the design and synthesis of scalemic  $\beta$ -amino sulfides<sup>7</sup> and herein we report the use of the sulfides **3-8** for the enantioselective addition of methylcuprates to 2-cyclohexen-1-one **1** (Scheme 1) and detail the X-ray absolute configuration analysis of  $[\mathbf{8Cu}(\mu\text{-I})_2\text{Cu}\mathbf{8}] \mathbf{11}$  (Figure 1).

Thus, two series of  $\beta$ -amino sulfides, one set derived from L-proline **3-5** and a second obtained from (*S*)-phenylglycine **6-8** were used in the enantioselective conjugate addition of methylolithium to 2-cyclohexen-1-one

1. The reactions were carried out by using scalemic ligands **3-8** (1.15 mmol), MeLi (2.38 mmol), copper(I) salt (1.15 mmol) in dry solvent (9 ml) at various temperatures (-45-0 °C). These conditions were chosen after careful study of the thermal stability of the cuprates and our results are presented in Table 1.

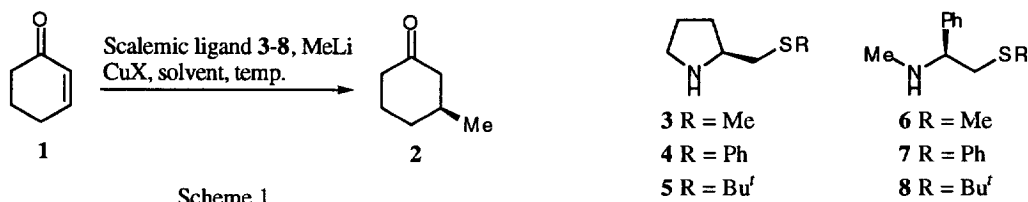


Table 1. Conjugate Addition of Scalemic Methylcuprate to **1** in the Presence of Ligands **3-8**

Entry	Ligand	X	Solvent	Temp. (°C)	Yield <sup>a</sup>	ee (config.) <sup>b</sup>
1	none	Br	Bu <sup>t</sup> OMe	0	55	0
2	<b>3</b>	Br	Bu <sup>t</sup> OMe	-45	36	0
3	<b>4</b>	Br	Bu <sup>t</sup> OMe	-40	42	16 ( <i>R</i> )
4	<b>5</b>	Br	Bu <sup>t</sup> OMe	0	14-33	0-64 ( <i>S</i> )
5	<b>5</b>	I	Bu <sup>t</sup> OMe	-40	15	0
6	<b>5</b>	I	Toluene	-40	36	11 ( <i>R</i> )
7	<b>6</b>	I	Ether	-40	33	13 ( <i>R</i> )
8	<b>6</b>	I	Toluene	-40	27	7 ( <i>S</i> )
9	<b>7</b>	I	Toluene	-40	42	20 ( <i>R</i> )
10	<b>8</b>	I	Ether	-40	34-46	0-9 ( <i>S</i> )
11	<b>8</b>	Br.SMe <sub>2</sub>	Ether	-40	39	6( <i>S</i> )
12	<b>8</b>	I	Toluene	-40	46	9-35( <i>R</i> )

<sup>a</sup> Isolated yield for chromatographically pure material (> 97 %). <sup>b</sup> Ees and absolute configuration determined by HPLC.

Several features of this study require further comment. Firstly, the ees for the ligands **3** (0% ee) and **4** (16% ee) are lower than those originally claimed by Dieter and Tokles (8-71% ee and 80% ee, respectively)<sup>4b</sup> but are more in line with the modified observations of these workers for prolinol ethers (0-56%).<sup>4a</sup> The ees reported herein and isolated yields are in accord with those obtained by other workers using N-heterocuprates (0-58% ee, 28-57% isolated yields)<sup>3,4</sup> for the conjugate addition of a methyl group to cyclohexenone **1**. Secondly, the ees obtained proved to be variable with some batches of methyl lithium giving high asymmetric induction while others gave none. This variability in ee has been observed previously<sup>2b,4a</sup> and the use of a series of additives (MeI, LiBr or Me<sub>3</sub>SiCl) in the reaction failed to overcome this variability. Thirdly, the use of toluene as the solvent leads to a preponderance of the opposite enantiomer to that observed when ethereal solvents are used (entries **4** vs **6**, **7** vs **8** and **10** vs **12**). This change in facial selectivity for N-heterocuprates on changing the solvent has been noted previously<sup>4b</sup> and is a consequence of the cuprate solvation and aggregation.

The scalemic ligands used were easily recovered by silica gel chromatography in yields of 53-64% without loss of enantiomeric excess. Moreover, when toluene was used as the solvent in the conjugate additions using phenylglycine derived ligands **6-8** then the corresponding dimeric copper iodide complexes  $[(\text{CuI})_2(\mathbf{6})_2]$  **9**,  $[(\text{CuI})_2(\mathbf{7})_2]$  **10**, and  $[\mathbf{8Cu}(\mu\text{-I})_2\text{Cu}\mathbf{8}]$  **11**, were isolated by silica gel chromatography. The complex **11**<sup>8</sup> provided crystals that were suitable for a single crystal X-ray study (Figure 1). The structure of complex **11** consists of discrete dimeric units of two different conformations with each conformation showing crystallography imposed  $C_2$  symmetry. These two conformations are broadly similar with a slight lengthening of the copper-copper distance (2.587(1) vs 2.650(2) Å) and a twist in the plane of the phenyl ring relative to the CuNCCS ring (-109.6(8) vs -119(1)°). The copper atoms display distorted tetrahedral geometries with nonplanar CuICuI rings typical of related thio complexes containing  $sp^2$  hybridized nitrogen donors.<sup>9</sup> However, dimer **11** is a thioether complex with  $sp^3$  hybridized nitrogen donors and represents the first example of a chiral amino sulfide ligand. Moreover, the absolute configuration of complex **11** was established by examining the anomalous scattering of Friedel mates and was confirmed by obtaining significantly better R factors for the indicated enantiomer. Thus, the stereochemistry at the stereogenic carbon of the ligand was confirmed as (*S*) while the configurations at the nitrogen and sulfur centres were established as being (*R*). This structure of complex **11** is being used as a basis for the design of improved ligands and in establishing the mechanism of chirality transfer using ligands **3-8**.

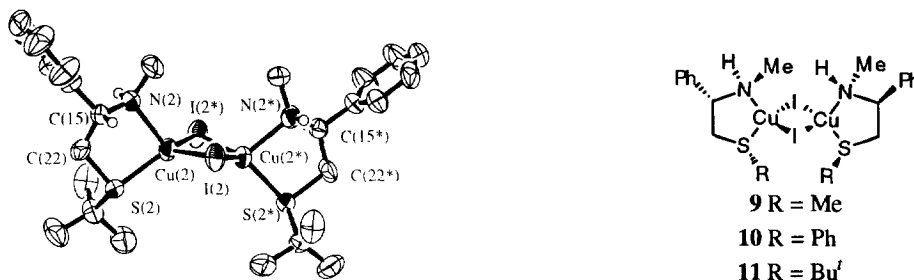


Figure 1 Molecular Structure of One Conformation of **11** with crystallographic numbering scheme.

In conclusion, two series of  $\beta$ -amino sulfides **3-5** and **6-8**, derived from *L*-proline and (*S*)-phenylglycine, respectively, have been used to prepare chiral *N*-heterocuprates. These chiral *N*-heterocuprates have been utilized in the enantioselective transfer of a methyl group to 2-cyclohexen-1-one **1**. The *tert*-butyl sulfide **5** ligand gave the highest ee of up to 64% for the preparation of (*S*)-3-methylcyclohexanone **2**. The  $\beta$ -amino sulfides **6-8**, derived from (*S*)-phenylglycine, gave relatively stable dimeric complexes with copper(I) iodide and an X-ray absolute configuration analysis of the complex **11** is reported.

**Acknowledgements:** We thank Shell Research Ltd. and the EPSRC for a CASE award (GAC). Grateful acknowledgement is made to the University of Strathclyde for funds for the purchase of the diffractometer and for a Science Capital Fund Starter Grant for the purchase of HPLC equipment. We warmly thank Mr. Alan Taylor (Edinburgh University) for the determination of the accurate mass of dimeric complex **11**.

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  - Selected data for **1**: mp 155-156 °C, found M<sup>+</sup> 825.9481, 827.9536 C<sub>26</sub>H<sub>42</sub>Cu<sub>2</sub>I<sub>2</sub>N<sub>2</sub>S<sub>2</sub> requires 825.9475, 827.9455; δ<sub>H</sub> (CDCl<sub>3</sub>, 250 MHz) 7.43-7.24 (m, 5H), 3.66 (dd, J 11.3, 4.3 Hz, 1H), 2.97-2.81 (m, 2H), 2.45 (s, 3H), 2.13 (br, 1H), 1.48 (s, 9H); δ<sub>C</sub> (CDCl<sub>3</sub>, 62.9 MHz) 140.7, 129.2, 128.3, 126.7, 64.9, 46.7, 38.3, 35.9, 30.6. Crystal data for **1**: C<sub>26</sub>H<sub>42</sub>Cu<sub>2</sub>I<sub>2</sub>N<sub>2</sub>S<sub>2</sub>, monoclinic, space group C2(#5), a = 19.749(2), b = 9.9393(9), c = 17.443(2) Å, β = 106.578(8)°, V = 3281.6(6) Å<sup>3</sup>, Z = 4, D<sub>c</sub> = 1.675 g cm<sup>-3</sup>, F(000) = 1632, μ(MoKα) = 0.71069 Å<sup>-1</sup>, colourless prism 0.4 x 0.25 x 0.2 mm. Data were collected at 22 ± 1 °C on a Rigaku AFC7S diffractometer using the ω-2θ to a maximum 2θ value of 54.0°. A total of 7816 reflections (7170 unique) were collected. The structure was solved by heavy-atom Patterson methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-square refinement was based on 4555 observed reflections (I > 2.00σ(I)) and reached R = 0.030 and R<sub>w</sub> = 0.036. The maximum peak in the final difference electron density map was 0.56 e Å<sup>-3</sup>. The absolute configuration of the structure was obtained by examining the anomalous scattering of Friedel mates and was confirmed by obtaining significantly better R factors for the given enantiomer. Selected bond lengths (Å), bond angles (°) and torsion angles (°): I(2)-Cu(2) 2.636(1), I(2)-Cu(2\*) 2.575(1), Cu(2)-Cu(2\*) 2.650(2), Cu(2)-S(2) 2.325(2), Cu(2)-N(2), 2.158(8), I(2)-Cu(2)-I(2\*) 117.47(3), I(2)-Cu(2)-S(2) 108.55(7), I(2)-Cu(2)-N(2) 105.6(2), I(2\*)-Cu(2)-S(2) 125.57(8), I(2\*)-Cu(2)-N(2) 106.7(2), S(2)-Cu(2)-N(2) 86.1(2), I(2)-Cu(2)-I(2\*)-Cu(2\*) 13.33(8), Cu(2)-I(2)-Cu(2\*)-S(2\*) -131.02(8) Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.
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