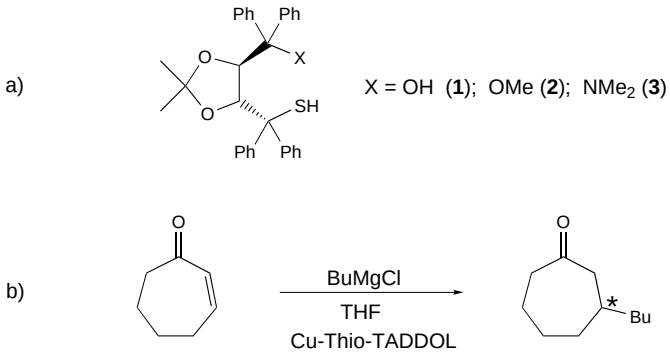
X-Ray, Molecular Diffusion, and NOESY NMR Studies of Chiral, Tetranuclear Cu^{I} Catalysts Based on Monodentate Thiol Analogues of TADDOL**

Arkadius Pichota, Paul S. Pregosin,* Massimiliano Valentini, Michael Wörle, and Dieter Seebach*

Chiral Lewis acid catalysts, and specifically homogeneously catalyzed conjugate addition reactions based on copper complexes, have been studied extensively in recent years.[1–3] Frequently, the metal is introduced as a simple salt, and occasionally as a preformed chelate complex. There is relatively little known about the structures of the metal complex intermediates which develop during the catalysis, especially when several metal centers are present.[4]

One of our groups[5] has reported on the enantioselective 1,4-addition of Grignard reagents to enones using CuCl and the thiols **1**–**3**. These ligands are O,S and N,S analogues of TADDOL a versatile and synthetically accessible chiral auxiliary.[6] During our investigations it was found that thiol **1** gives rise to preferential formation of (−)-(*S*)-3-butylcycloheptanone, whereas **2** or **3** afford mainly (+)-(*R*)-3-butylcycloheptanone from cycloheptenone and BuMgCl (Scheme 1).[5]



Scheme 1. a) Thiol-TADDOL ligands **1**–**3**. b) Copper-catalyzed conjugate addition: e.r. = 92:8 (with **1**), e.r. = 8:92 (with **2** or **3**).

We report here on a novel catalyst intermediate which is shown to be a tetranuclear, monodentate copper thiolate complex—that is, the second donor atom of the TADDOL derivative is not complexed. This is unprecedented in that it is commonly thought that such auxiliaries act as bidentate ligands. Moreover, we suggest a) that this species retains its tetranuclear structure in solution upon addition of a model substrate, based on NMR diffusion measurements and b) that the selectivity inversion is based on structural differences in the tetranuclear species as shown by 2D ^{1}H NOE NMR spectroscopy.

The unexpected inversion in stereoselectivity as a function of auxiliary prompted us to determine the relationship between the enantiopurity of the product and that of the ligands **1** and **2**[7] (Figure 1). The observed deviation from linearity is modest; nevertheless, these results suggest that

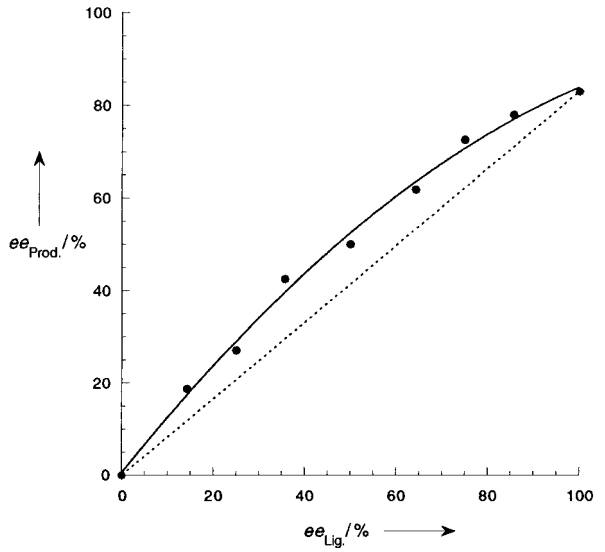
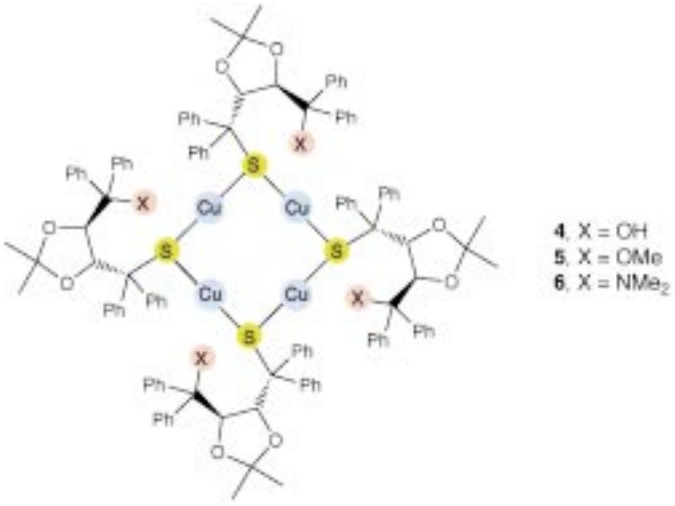


Figure 1. Observed positive nonlinear effect (NLE) for the copper-catalyzed 1,4-addition of BuMgCl to cycloheptenone using ligand **1**. A weaker, but still positive NLE, is observed with ligand **2**.[5]

more than one ligand (and perhaps several metals) might be involved in the catalysis.[8] Since higher molecular weight copper thiolates used in catalysis are isolable,[9] we considered the copper coordination chemistry of **1**–**3**. Reaction of these auxiliaries with BuLi followed by addition of CuCl affords the tetranuclear copper thiolate complexes **4**–**6** in good yields.



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[**] TADDOL = α,α,α′,α′-tetraaryl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol.

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Complex **4** can also be obtained—as an air-stable, crystalline material—by heating CuCl, **1**, and Et_3N at reflux in MeOH.

Complexes **4**–**6** show the same reactivity and selectivity previously observed for the in situ procedures.[5] Consequently, they are either precursors or catalytically active species in this conjugate addition.

The solid-state structure of **4** was determined by X-ray diffraction methods (Figure 2). The complex contains a butterfly-type arrangement of the Cu_4S_4 core, although the

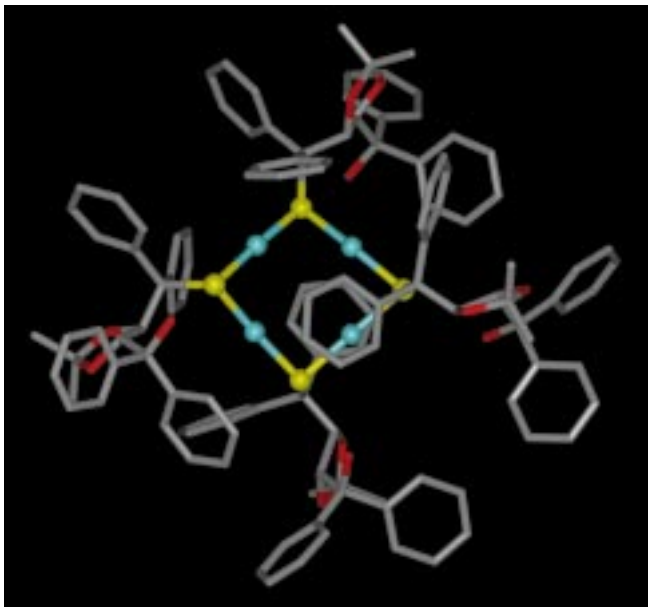

Figure 2. Structure of the tetranuclear Cu complex **4** based on X-ray diffraction data. The H atoms have been omitted for clarity; O atoms are indicated in red, S atoms in yellow, and Cu atoms in blue. The view has been generated with the program insight II (v. 98.0).

four metal atoms lie almost in a plane. Two Cu–Cu separations are relatively short (ca. 2.8 Å), and two are somewhat longer (ca. 3.0 Å). Each of the copper atoms is coordinated to two bridging thiolate sulfur donors (Cu–S 2.14–2.19 Å, S-Cu-S ca. 166 and ca. 177°), thus leaving each Cu^I center coordinatively unsaturated.[10] The oxygen atom of the OH group is not complexed, based both on the very long O···Cu distances in the structure (3.9–4.3 Å) and the NMR signal observed for the OH proton in solution ($\delta \approx 8.7$). Consequently, this TADDOL-derived thiol is functioning as a monodentate and not a bidentate ligand for Cu^I. The same conclusion is reached for **5** and **6** based on NMR studies. We know of no documented example of a "successful" bidentate chiral auxiliary which functions as a monodentate ligand in enantioselective catalysis. The solid-state data show two different ligand environments per tetranuclear complex, and for the OMe analogue **5** this has been confirmed in solution by ^{1}H NMR measurements at 213 K.

In an attempt to prepare models related to our copper chemistry, we allowed **4**–**6** to react with an excess of *tert*-butylisocyanide in [D_8]THF to afford the corresponding isocyanide complexes **7**–**9**. These new compounds, generated in situ, show exchange of the isocyanide ligands in solution; however, ^{1}H NMR pulsed-gradient diffusion measurements[11, 12] on **7**–**9** reveal that these are also tetranuclear species (Figure 3). Diffusion measurements reflect molecular motion in solution and thus are sensitive to molecular weight. We used the measured diffusion data for the ligands **1** and **2**, which exist as a hydrogen-bonded dimer and monomer,

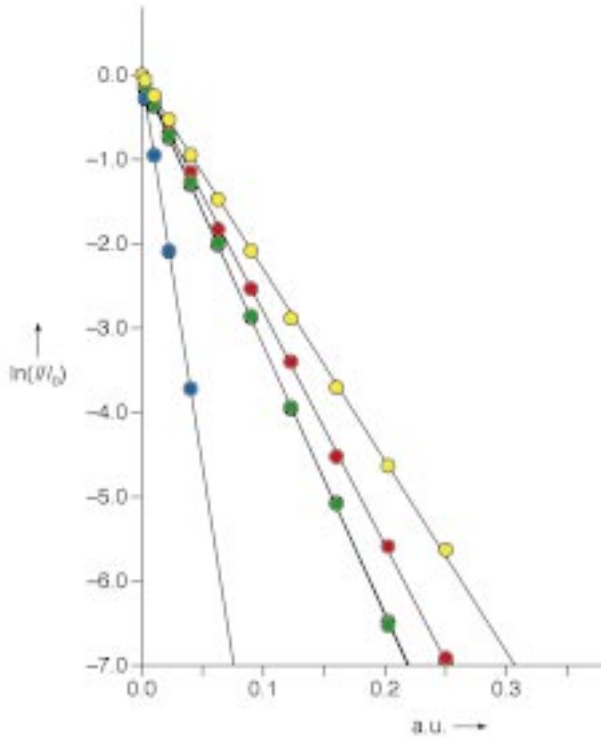

Figure 3. Results of the diffusion measurements using pulsed-field gradients[11] for the isocyanide complex **7** (yellow), the ligand **1** (red), ligand **2** (green), and solvent THF (blue). The slopes are proportional to the diffusion coefficient (D) and to the hydrodynamic radii of **7**, **1**, **2**, and THF. The y axis represents a measure of the relative spin–echo signal intensity, and the x axis represents the square of the gradient amplitude in arbitrary units (a.u.).

respectively, as reference for **7**–**9**. The results confirm that **4**–**6** do not degrade to mononuclear species in the presence of additional ligands. To the best of our knowledge, this represents the first application of NMR diffusion measurements for the determination of the aggregation state[13] of transition metal catalysts.

Despite the exchange, the residence time of the isocyanide donor in **7**–**9** is sufficient such that ^{1}H NOE NMR spectroscopy[14] detects a variety of contacts from the complexed thiolate ligand to the *tert*-butyl group of the isocyanide (Figure 4). Analysis of these spectra suggests a different structure for **7** relative to **8** (and **9**). For **7** the NOE data clearly point to a structure in which the noncomplexed OH-containing section of the molecule has been rotated so as to bring the OH and *ortho* phenyl protons of one of the two rings in close proximity to the Cu center (Scheme 2). This is in contrast to the NOESY data for **8** and **9**, which suggest that the methoxy and dimethylamino groups remain remote from the metal.[15] These structural differences create a different chiral environment around the copper atom and may be the source of the observed stereochemical inversion noted above.

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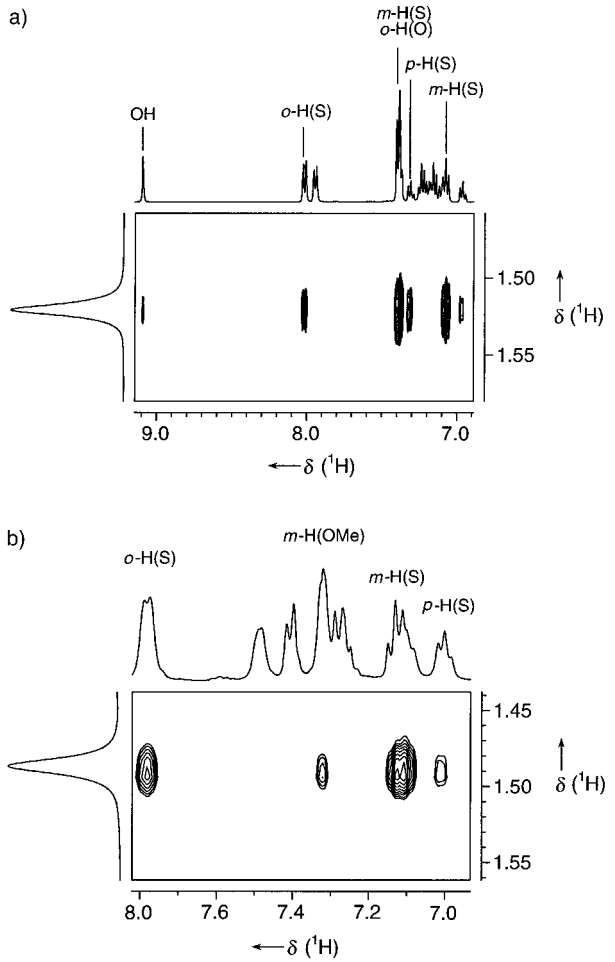
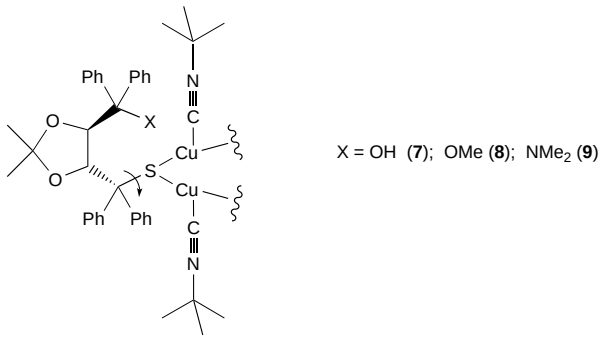


Figure 4. Sections of the NOESY NMR spectrum for the isocyanide complexes **7** (a) and **8** (b). In (a) there are NOEs from the OH proton and the *ortho*-phenyl protons of one of the phenyl rings of the $Ph_2C(OH)$ moiety to the methyl protons of the isocyanide. In (b) the only strong NOEs arise from the *ortho*-phenyl protons of one of the proximate $Ph_2C(S)$ rings to the methyl protons of the isocyanide. The dynamics for **7** are slightly different than for **8**. The letters in parenthesis (O, S, and OMe) refer to aryl protons of the $Ph_2C(OH)$, $Ph_2C(S)$, and $Ph_2C(OMe)$ groups, respectively (400 MHz, [D_8]THF, ambient temperature, $\tau = 650-800$ ms).



Scheme 2. Fragment showing the rotation around the C–S bond. This rotation brings the OH group and the corresponding phenyl rings closer to the isocyanide ligand.

Concluding, we find that the Cu-catalyzed enantioselective conjugate addition with ligands **1**–**3** proceeds via a tetranuclear species which uses an unprecedented monodentate complexation mode. Diffusion measurements are shown to be valuable for the determination of the aggregation state of organocopper complexes in solution.

Experimental Section

Crystal structure analysis of **4**: $C_{124}H_{116}Cu_4O_{12}S_4+C_{6.75}$, $M_r = 2261.64$, colorless crystal ($0.3 \times 0.26 \times 0.08$ mm^3). Suitable crystals were obtained from THF/hexane at 5 °C. A single crystal was sealed in a glass capillary and cooled to −35 °C. A data set covering a full sphere up to $2\theta = 46.50°$ was collected on a Siemens SMART platform diffractometer equipped with a CCD detector ($Mo_{K\alpha}$ radiation, graphite monochromator, ω scans with 0.3° step width). Data reduction and corrections for Lorentz polarization and absorption ($\mu = 0.761$ mm^{-1}, min./max. transmission 0.9416/0.8038) were performed using the programs SAINT[16] and SADABS.[17] The structure was solved by direct methods and refined by full-matrix least squares (versus F^2) with the SHELXTL program package:[17] orthorhombic, space group $P2_12_12$; $a = 20.768(3)$, $b = 40.580(6)$, $c = 15.467(2)$ Å, $V = 13035(3)$ Å^3; $Z = 4$; of 69777 reflections, 18575 were independent ($R_{int} = 0.1135$); $R1 = 0.0707$, $wR2 = 0.1625$ for 1388 parameters and 12070 reflections with $I > 2\sigma(I)$. The residual electron density was 0.447 and −0.416 e Å^{-3}. All non-hydrogen atoms, except the atoms belonging to disordered solvent molecules, were refined with anisotropic thermal parameters for each group, and all hydrogen atoms were placed at calculated positions and refined with common isotropic thermal parameters for each group. Several disordered solvent molecules were described with partially occupied C atom positions. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-125017. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Acetyl Substitution of the O-Specific Caryan from the Lipopolysaccharide of *Pseudomonas (Burkholderia) caryophylli* Leads to a Block Pattern**

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Most of the O-specific polysaccharides of lipopolysaccharides (LPS) from Gram-negative bacteria represent heteropolysaccharides furnished with repeating units that comprise between two and eight monosaccharidic residues.[1] A large variety of sugars has been identified in such O-specific polysaccharides, which additionally may be phosphorylated, methylated, substituted by amino acids, or acetylated. Especially the last decoration has been frequently identified; it is always present in nonstoichiometric amounts. The acetylation takes place in later steps of O-specific polysaccharide biosynthesis and has been discussed as a microheterogenic property of LPS. In some cases, homopolysaccharides have been identified as O-specific polysaccharides which are mainly furnished from (amino-)deoxy sugars that may be N- and/or O-acylated, thus resulting in rather hydrophobic molecules.[2, 3] However, the influence of O-acetyl groups on the conformation of O-specific polysaccharides in general and on the establishment of O-antigenic conformative epitopes has not been investigated.

Few bacteria possess LPS that contain two different O-specific polysaccharides. In particular, this phenomenon is typical for *Burkholderia*,[3] a genus that comprises species which are pathogenic either to humans or plants. *Pseudomonas* (*Burkholderia) caryophylli* is a phytopatogenic bacterium responsible for the wilting of carnation.[4] Its LPS contain two linear homopolysaccharides as O-specific polysaccharides that are built up by two novel and rather peculiar monosaccharides. The major LPS portion possesses a polysaccharide termed caryophyllan, consisting of α-(1 $\rightarrow$7)-linked caryophyllose (3,6,10-trideoxy-4-*C*-(D-*glycero*-1-hydroxyethyl)-D-*erythro*-D-*gulo*-decose).[5–7] The minor LPS portion contains a polysaccharide named caryan, built up from β-(1 $\rightarrow$7)-linked caryose (4,8-cyclo-3,9-dideoxy-L-*erythro*-D-*ido*-nonose).[7, 8] These O-specific polysaccharides are thought to be involved

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