In search of enantioselective catalysts for the Henry reaction: are two metal centres better than one?†

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Catalysts for the asymmetric Henry reaction involving copper(II) complexes of the chiral Schiff bases *N*,*N*′-(1*R*,2*R*)-(−)-1,2-cyclohexylenebis(3-hydroxysalicylideneamine) (H_2**1**) and *N*,*N*′-(1*R*,2*R*)-(−)-1,2-cyclohexylenebis(3-ethoxysalicylideneamine) (H_2**2**), and H_2**3**, which is the reduced analogue of H_2**1**, have been studied. Whereas [Cu(**1**)] and [Cu(**2**)] give poor yields and enantioselectivity, [Cu(**3**)] produced moderate to high yields and enantioselectivities were optimal when reactions were carried out in toluene rather than a polar solvent. A significant finding is that both yield and enantioselectivity are enhanced when a second equivalent of $Cu(OAc)_2$ is added to the catalyst. The single-crystal structures of [Cu(**3**)] and [Cu(**1**)(H_2O)] are presented, and the host–guest interactions and molecular packing in the latter are compared with those in [Cu(**2**)(H_2O)].

Introduction

The Henry (nitroaldol) reaction is an important carbon–carbon bond forming reaction in synthetic chemistry.[1–3] The resultant β-hydroxy nitro compounds are useful precursors for the synthesis of biologically significant building blocks including chiral β-amino alcohols and α-hydroxyl carboxylic acids.[2–6] Over the last few years, attention has focused on enantioselective Henry reactions,[7–10] and among the catalysts employed have been a variety of chiral copper(II),[10–22] copper(I),[23,24] cobalt(II)[25] and chromium(III)[26] complexes. In addition to the selectivity required of a catalyst, it is advantageous for it to be insensitive to air and moisture, easy to prepare and inexpensive. It is also desirable to have mild reaction conditions and no requirement for the addition of organic bases. Copper(II) catalysts are proving to be the most successful in the asymmetric Henry reaction, and enantioselectivities reported to date range from moderate to high.[10–22] We recently described the synthesis and structural characterization of the copper(II) Schiff base complex [Cu(**2**)(H_2O)] where H_2**2** is *N*,*N*′-(1*R*,2*R*)-(−)-1,2-cyclohexylenebis(3-ethoxysalicylideneamine) (Scheme 1).[27] This chiral complex is formed under mild conditions and in near quantitative yield. Here we report the facile formation of two related chiral copper(II) complexes, and the performance of all three complexes as catalysts in an asymmetric Henry reaction.

Experimental

General

Commercially available chemicals were reagent grade and were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX-400 spectrometer; chemical shifts for ^{1}H and ^{13}C NMR spectra are referenced to residual solvent peaks with respect to TMS = δ 0 ppm. Infrared spectra were recorded on a Shimadzu FTIR-8400S spectrophotometer with solid samples on a Golden Gate diamond ATR accessory. Electronic absorption spectra were recorded on a Varian-Cary 5000 spectrophotometer. Electrospray mass spectra were recorded using a Finnigan MAT LCQ mass spectrometer. HPLC was carried out using an intelligent pump, detector and integrator on a Hewlett Packard S1100 instrument using a Chiralcel OD–H column (85 : 15, heptane–isopropanol, 0.8 cm^3 min^{-1}, 230 nm).

Ligands H_2**1**[28] and H_2**2**[29] (Scheme 1) and complex [Cu(**2**)][27] were prepared as previously reported. (1*R*,2*R*)-(−)-1,2-diaminocyclohexane and 3-ethoxysalicylaldehyde were used as received (Fluka or Sigma-Aldrich).

Synthesis of $H_2$3

A solution of (1*R*,2*R*)-(−)-1,2-diaminocyclohexane (0.228 g, 2.00 mmol) in methanol (10 cm^3) was added dropwise to a stirring solution of 3-ethoxysalicylaldehyde (0.665 g, 4.00 mmol) in methanol (20 cm^3). The mixture was heated to reflux for 2 h, and then cooled to room temperature. Solid $NaBH_4$ (0.38 g, 10 mmol) was added in small portions over a period of 1 h, and the resulting colourless solution was stirred overnight at room temperature. Solvent was removed under reduced pressure, and water (100 cm^3) was added. The product was extracted with CH_2Cl_2 (3 × 60 cm^3); the combined organic phases were washed with water and brine, and dried over Na_2SO_4. The solution was filtered and evaporated under reduced pressure to dryness to give colourless oil which was purified by column chromatography (SiO_2, hexane–EtOAc 3 : 1 with 5% MeOH). H_2**3** was isolated as a white solid (0.73 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm 6.76 (dd, J = 8.0, 1.6 Hz, 2H, $H^{A4/6}$), 6.70 (t, J = 7.7 Hz, 2H, H^{A5}), 6.64 (dd, J = 7.6, 2.0 Hz, 2H, $H^{A4/6}$), 4.06 (q, J = 7.0 Hz, 4H,

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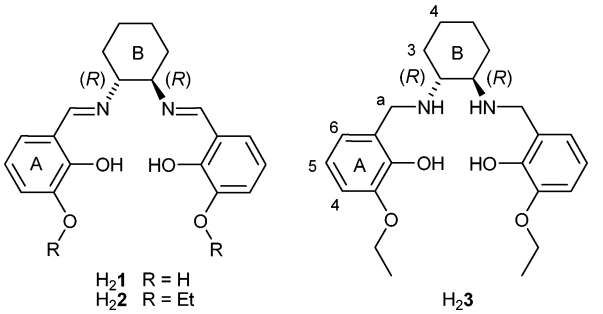


Scheme 1 Structures of ligands and labelling for NMR spectroscopic assignments for H_2**3**.

$H^{CH_2CH_3}$), 3.99 (d, J = 13.5 Hz, 2H, H^a), 3.83 (d, J = 13.5 Hz, 2H, $H^{a\prime}$), 2.38 (m, 2H, H^B), 2.11 (m, 2H, H^B), 1.67 (m, 2H, H^B), 1.43 (t, J = 7.0 Hz, 6H, $H^{CH_2CH_3}$), 1.21 (m, 4H, H^B). ^{13}C NMR ($CDCl_3$, 400 MHz) δ/ppm 147.1, 146.7, 124.4, 120.9, 119.1, 112.1, 64.5, 60.8, 48.9, 30.7, 24.6, 15.2. ESI-MS (MeOH) m/z 415.3 [M + H^+] (base peak, calc. 415.3), 437.1 [M + Na^+] (calc. 437.2). UV/VIS λ_{max}/nm (1.45 × 10^{-4} mol dm^{-3}, THF) 236 ($\varepsilon/10^3$ dm^3 mol^{-1} cm^{-1} 4.6), 280 (3.0). FT-IR (solid, cm^{-1}): 2936m, 1584m, 1471s, 1393m, 1279s, 1241s, 1116s, 1073s, 988w, 963w, 948w, 905w, 887m, 839w, 832w, 724s. Found C 68.74, H 8.16, 6.27; $C_{24}H_{34}N_2O_4 \cdot 1/3H_2O$ requires C 68.54, H 8.31, N 6.66%. $[\alpha]_D^{20}$ = −73.5 (c = 0.5, CH_2Cl_2).

Synthesis of [Cu(1)]

An aqueous solution (3 cm^3) of $Cu(OAc)_2$ (18.1 mg, 0.100 mmol) was added to a stirring solution of H_2**1** (35.4 mg, 0.100 mmol) in MeOH (10 cm^3) at room temperature. The purple solution was stirred for 2 h, and then allowed to evaporate slowly at room temperature. After 2 d, the brown precipitate that had formed was collected by filtration, washed with Et_2O and dried *in vacuo*. [Cu(**1**)] was isolated as a brown crystalline solid (40.2 mg, 0.0967 mmol, 96.7%). ESI-MS (MeOH) m/z 438.4 [M + Na^+] (base peak, calc. 438.1), 853.2 [2M + Na^+] (calc. 853.1). UV/VIS λ_{max}/nm (9.47 × 10^{-5} mol dm^{-3}, THF) 249 ($\varepsilon/10^3$ dm^3 mol^{-1} cm^{-1} 24.3), 284 (23.6), 379 (5.75), 566 (0.28). FT-IR (solid, cm^{-1}): 3484m, 2937m, 1622s, 1552m, 1447s, 1384m, 1345w, 1317s, 1236s, 1090w, 1025m, 868m, 735s, 668m. Found C 54.38, H 5.00, 6.36; $C_{20}H_{20}CuN_2O_4 \cdot 3/2H_2O$ requires C 54.23, H 5.23, N 6.32%.

Synthesis of [Cu(3)]

A solution of $Cu(OAc)_2$ (18.1 mg, 0.100 mmol) in MeOH (5 cm^3) was added to a stirring solution of H_2**3** (41.4 mg, 0.100 mmol) in MeOH (10 cm^3) at room temperature. The green solution was stirred for 30 min, and was then evaporated under reduced pressure to dryness. The solid was washed well with Et_2O, and then dried *in vacuo*. [Cu(**3**)] was isolated as an orange–brown powder (46.9 mg, 0.0985 mmol, 98.5%). UV/VIS λ_{max}/nm (8.84 × 10^{-5} mol dm^{-3}, THF) 251 ($\varepsilon/10^3$ dm^3 mol^{-1} cm^{-1} 16.5), 289 (10.6), 342 (1.19), 410 (1.21), 597 (0.39). FT-IR (solid, cm^{-1}): 3196w, 2932m, 1588w, 1564w, 1469s, 1423w, 1284m, 1233s, 1165w, 1115m, 1077s, 1044s, 925w, 904w, 844m, 737s. ESI-MS (MeOH) m/z 498.4 [M + Na^+] (base peak, calc. 498.2). Found C 59.16, H 6.76, N 5.47; $C_{24}H_{32}CuN_2O_4 \cdot {}^1/_2H_2O$ requires C 59.43, H 6.86, N 5.78%.

Typical procedure for asymmetric Henry reaction

Complex [Cu(**3**)] (4.76 mg, 0.01 mmol) was dissolved in toluene (0.4 cm^3) in a screw-capped vial containing a magnetic stirrer bar at room temperature. The reaction solution was stirred for 10 min before $Cu(OAc)_2$ (1.81 mg, 0.01 mmol) was added. The deep-green solution was stirred for another 30 min, after which time $MeNO_2$ (0.13 cm^3, 1.0 mmol) and 4-nitrobenzaldehyde (0.2 mmol, 1.0 equiv.) were added sequentially. The mixture was allowed to stir at room temperature for 60 h. The volatile components were removed under reduced pressure and the crude product was purified by column chromatography (SiO_2, hexane–EtOAc, 3 : 1, v/v) to give the nitroaldol product **4**, isolated as a pale-yellow solid (26 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm 8.27 (d, 2H, J = 8.8 Hz, H^{Ar}), 7.63 (d, 2H, J = 8.4 Hz, H^{Ar}), 5.61 (m, 1H, H^{CHOH}), 4.61 (dd, 1H, J = 14.0, 8.4 Hz, H^{CH_2}), 4.56 (dd, 1H, J = 13.6, 4.0 Hz, H^{CH_2}), 3.14 (d, 1H, J = 4.0 Hz, H^{OH}). The enantiomeric excess was determined by HPLC: minor enantiomer t_r = 19.0 min, major enantiomer t_r = 23.3 min; 77% ee; $[\alpha]_D^{20}$ + 15.2 (c 0.5, CH_3OH). The absolute configuration of Henry product was assigned as (*S*) by comparison of its optical rotation with literature values.[30]

Crystal structure determinations

Data were collected on a Bruker-Nonius Kappa CCD instrument; data reduction, solution and refinement (on F(obs)) used the progammes COLLECT,[31] DENZO/SCALEPACK,[32] SIR92[33] and CRYSTALS.[34] Structures have been analysed using Mercury v. 1.4.2.[35] ORTEP figures were drawn using Ortep-3 for Windows.[36]

[Cu(1)(H_2O)]

$C_{20}H_{22}CuN_2O_5$, M = 433.95, purple plate, monoclinic, space group $P2_1$, a = 7.9835(3), b = 20.8163(7), c = 11.0230(4) Å, β = 101.777(2)°, U = 1793.3(1) $Å^3$, Z = 4, D_c = 1.607 Mg m^{-3}, μ(Mo-K_α) = 1.255 mm^{-1}, T = 173 K, 12 420 reflections collected. Refinement of 8548 reflections (506 parameters) with $I > 3\sigma(I)$ converged at final R_1 = 0.0235 (R_1 all data = 0.0412), wR_2 = 0.0262 (wR_2 all data = 0.0370), R_{int} = 0.033, gof = 1.067, Flack parameter = 0.004(7).

[Cu(3)]

$C_{24}H_{32}CuN_2O_4$, M = 476.08, red block, triclinic, space group $P1$, a = 8.8481(3), b = 11.8842(4), c = 11.9786(4) Å, α = 96.919(2), β = 106.430(2), γ = 109.055(2)°, U = 1110.04(7) $Å^3$, Z = 2, D_c = 1.424 Mg m^{-3}, μ(Mo-K_α) = 1.017 mm^{-1}, T = 123 K, 13 379 reflections collected. Refinement of 7017 reflections (560 parameters) with $I > 3\sigma I$) converged at final R_1 = 0.0452 (R_1 all data = 0.1012), wR_2 = 0.0470 (wR_2 all data = 0.0877), R_{int} = 0.041, gof = 1.175, Flack parameter = 0.04(2).

Results and discussion

Synthesis and structures of catalysts

We recently reported the structure of [Cu(**2**)(H_2O)], which exhibits host–guest, hydrogen-bonded recognition of H_2O in the *O*,*O*′,*O*″,*O*‴-cavity of [Cu(**2**)].[27] In addition to structural aspects of this class of compound,[27] we were also interested in testing them as selective asymmetric catalysts. We have therefore prepared complexes [Cu(**1**)] and [Cu(**3**)], which comprise a series of chiral copper(II) complexes that vary either in the size of the *O*,*O*′,*O*″,*O*‴-cavity or in having an unsaturated or saturated backbone. Ligands H_2**1**[28] and H_2**2**[29] have previously been reported. Ligand H_2**3** (Scheme 1) was prepared by the condensation of (1*R*,2*R*)-(−)-1,2-diaminocyclohexane with 3-ethoxysalicylaldehyde, followed by reduction with $NaBH_4$, and was characterized by routine spectroscopic methods. The reactions of equimolar amounts of $Cu(OAc)_2$ with enantiopure ligands H_2**1** or H_2**3** result in the formation of [Cu(**1**)] or [Cu(**3**)], respectively, in high yield. The base peak in the electrospray mass spectrum of each complex corresponded to $[M + Na]^+$ (*m*/*z* 438.1 for [Cu(**1**)], 498.4 for [Cu(**3**)]). The electronic absorption spectra of a THF solution of each complex exhibited a low intensity MLCT band (566 nm for [Cu(**1**)], 597 nm for [Cu(**3**)]), in addition to more intense absorptions at higher energy assigned to ligand π* ← π transitions.

Single crystals of [Cu(**1**)(H_2O)] suitable for X-ray diffraction were grown by slow evaporation of a CH_2Cl_2–MeOH solution of [Cu(**1**)] over a period of 3 days. The complex crystallizes in the chiral space group *P*1, and one of the two independent molecules is shown in Fig. 1. Important bond parameters for both molecules are given in the figure caption. The coordination sphere around each of atoms Cu(1) and Cu(2) is close to being square planar; the donor atoms N1, N2, O1 and O3 lie ±0.06 Å out of the least squares plane through them, while around Cu(2), donor atoms N3, N4, O5 and O7 lie ±0.12 Å out of the corresponding least squares plane. Each pair of Cu(**1**)$_2$ units in the asymmetric unit assembles in a face-to-face arrangement (Fig. 2). Although the distance between pairs of aryl rings containing atoms C1 and C21, and C20 and C40, is ≈3.6 Å, the rings are offset and any π-stacking is therefore weak. Within the asymmetric unit, the Cu1···Cu2 separation is 3.6945(4) Å. While shorter than that observed in [Cu(**2**)(H_2O)] (3.816(1)Å),[27] the interaction in [Cu(**1**)(H_2O)] must be considered weak. However, the recurrence of this packing unit in both [Cu(**1**)(H_2O)] and [Cu(**2**)(H_2O)] indicates that the weak π-stacking and Cu···Cu interactions favourably reinforce one another. The water molecule in [Cu(**1**)(H_2O)] is hydrogen bonded within the *O*,*O*′,*O*″,*O*‴-cavity, in a similar manner to that observed in [Cu(**2**)(H_2O)].[27] However, the molecular packing in the two structures is markedly different, and can be rationalized in terms of the differences in which the hydroxy and ethoxy substituents, respectively, in [Cu(**1**)] and [Cu(**2**)] interact with the H_2O molecule (Scheme 2, hydrogen atoms were located). In addition to being a guest within the Cu(**2**) host, the water molecule is hydrogen bonded to a hydroxy substituent of an adjacent molecule (Fig. 3). The result is that stacks of [Cu(**1**)(H_2O)] units are organized in a herringbone fashion, in contrast to the parallel stacking in [Cu(**2**)(H_2O)][27] and [Cu(**3**)] (see below).

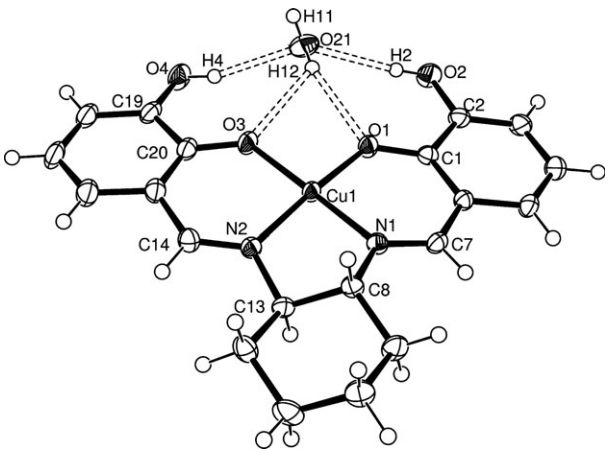


Fig. 1 Molecular structure of one of the crystallographically independent Cu(**1**)(H_2O) units in [Cu(**1**)(H_2O)] with ellipsoids plotted at the 50% probability level. Selected bond distances and angles: Cu1–N1 = 1.934(2), Cu1–N2 = 1.942(2), Cu1–O1 = 1.899(2), Cu1–O3 = 1.900(2), N1–C7 = 1.286(3), N1–C8 = 1.473(3), N2–C13 = 1.479(2), N2–C14 = 1.289(2) Å; N1–Cu1–N2 = 84.55(8), N1–Cu1–O1 = 94.65(7), O1–Cu1–O3 = 87.05(7), N2–Cu1–O3 = 93.88(7)°. For the second independent molecule, corresponding parameters are: Cu2–N3 = 1.933(2), Cu2–N4 = 1.945(2), Cu2–O5 = 1.910(2), Cu2–O7 = 1.898(2), N3–C27 = 1.286(3), N3–C28 = 1.475(2), N4–C33 = 1.482(3), N4–C34 = 1.279(3) Å; N3–Cu2–N4 = 84.89(8), N3–Cu2–O5 = 94.06(7), O5–Cu2–O7 = 87.75(7), N4–Cu2–O7 = 94.06(7)°.

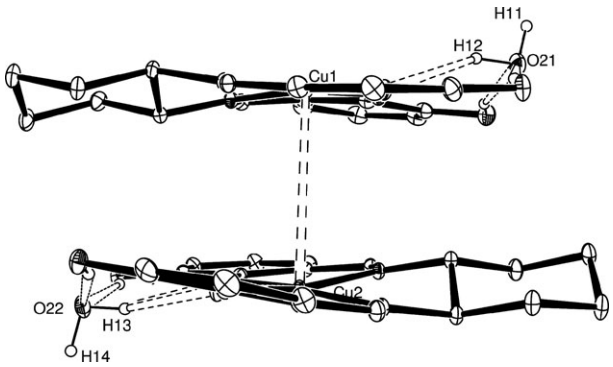
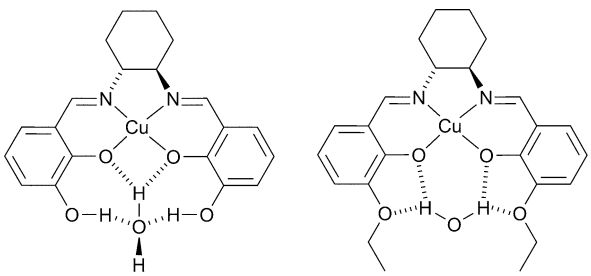


Fig. 2 Face-to-face stacking of a pair of crystallographically independent Cu(**1**)(H_2O) units in [Cu(**1**)(H_2O)]; Cu1···Cu2 = 3.6945(4) Å.



Scheme 2 Comparison of host–guest interactions in [Cu(**2**)(H_2O)] and [Cu(**1**)(H_2O)].

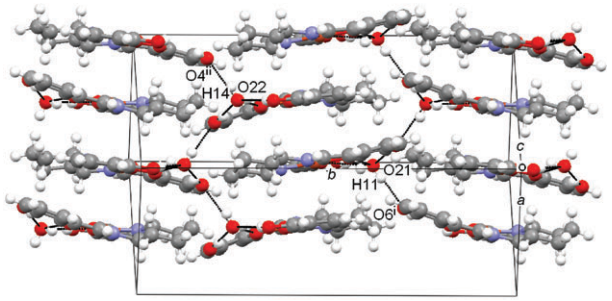


Fig. 3 Packing of molecules in [Cu(**1**)(H_2O)] showing hydrogen bonding interactions; symmetry codes: i = 1 − x, 1/2 + y, 1 − z; ii = −x, −1/2 + y, 1 − z.

X-Ray quality crystals of [Cu(**3**)] were grown over a period of a week by slow diffusion of Et_2O into an EtOH solution of the complex. Crystallization without a guest water molecule contrasts with the observations for [Cu(**1**)(H_2O)] and [Cu(**2**)(H_2O)]. [Cu(**3**)] crystallizes in the chiral space group $P1$, and there are two crystallographically independent molecules in the asymmetric unit, one of which is shown in Fig. 4. The two molecules pack face-to-face, but are significantly offset with respect to one another leading to a longer Cu1···Cu2 separation (4.443(2) Å) than in [Cu(**1**)(H_2O)]. The coordination environments of Cu1 and Cu2 deviate more from planarity than in [Cu(**1**)(H_2O)], with the sets of donor atoms being ±0.30 and ±0.18 Å out of the least squares plane through them. The lack of a guest molecule in the O,O',O'',O'''-cavity means that the ethoxy groups are less constrained than in [Cu(**2**)(H_2O)],[27] and, as a result, lie above and below the coordination plane. Molecules of [Cu(**3**)] pack in parallel stacks, with the most dominant intermolecular interactions being NH···O hydrogen bonds (N51H3···O1 = 2.11, N51···O1 = 2.956(2) Å, N51–H3···O1 = 161°; N52H4···$O2^i$ = 2.06, N52···$O2^i$ = 2.904(2) Å, N52–H4···$O2^i$ = 160°; symmetry code i = 1 + x, y, z). The only interactions between stacks are repulsive, close H···H contacts.

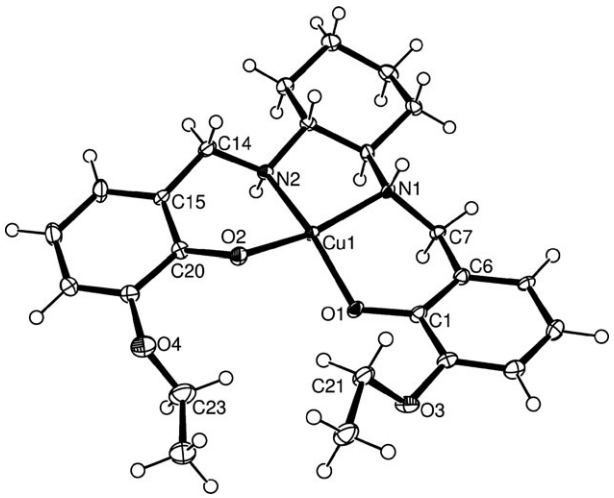


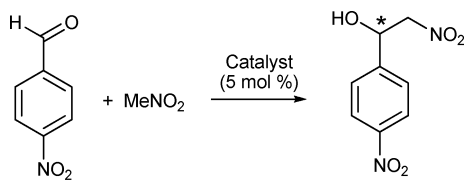
Fig. 4 Molecular structure of one of the crystallographically independent [Cu(**3**)] complexes with ellipsoids plotted at the 40% probability level. Selected bond distances and angles: Cu1–N1 = 2.006(6), Cu1–N2 = 2.014(5), Cu1–O1 = 1.913(5), Cu1–O2 = 1.915(5), N1–C7 = 1.473(7), N2–C14 = 1.454(8) Å; N1–Cu1–N2 = 85.4(2), N1–Cu1–O1 = 95.1(2), N2–Cu1–O2 = 93.9(2), O1–Cu1–O2 = 91.0(2)°. Bond parameters for the second molecule are similar.

Catalytic studies

The catalytic activities of the chiral copper(II) complexes [Cu(**1**)], [Cu(**2**)] and [Cu(**3**)] in the Henry reaction shown in Scheme 3 were tested both in the absence and presence of added metal salts. The enantiomeric excess of the product was determined by HPLC, and the results are presented in Table 1. All reactions were performed on a 0.20 mmol scale with 5 mol% of catalyst at a 0.5 M concentration using 5 equiv. of nitromethane in solvents indicated in Table 1. Reactions (except for one, see Table 1) were carried out at room temperature over a period of 60 h. The absolute configuration of the β-hydroxynitroalkane was assigned as (*S*) by comparison of the optical rotation with literature data.[30]

Initial reactions were carried out using copper(II) complexes of the Schiff base ligands H_2**1** and H_2**2** in ethanol. No or negligible enantioselectivity was observed. In an investigation of the activities of copper(II) complexes of ligands **5** and **6** and related oligothienyl ligands, as catalysts in asymmetric Henry reactions, Bandini *et al.*[20] have observed that saturated **6** produces significantly higher ee's than the unsaturated **5** (Scheme 4). Similarly, Blay and co-workers[21,22] have shown that, whereas $Cu(OAc)_2$ and imine **7** catalyse a Henry reaction giving products in high yields but moderate enantioselectivities, the use of copper(II) with the saturated ligand **8** leads to an enhancement of the enantioselectivity (Scheme 5). In accordance with these observations, we have found that, under the same conditions as the reactions using [Cu(**1**)] and [Cu(**2**)], [Cu(**3**)] produced both higher yields and enantioselectivity (Table 1). We therefore focused our attentions on [Cu(**3**)]. The effects of solvent were examined, and the highest ee (48%) was obtained in toluene rather than in a polar solvent. However, this was at the expense of yield (Table 1).

Structural data for complexes formed between copper(II) and ligands H_2**1** (see above) and H_2**2**[27] confirm the ability of the O,O',O'',O'''-cavity to host a water molecule. More relevant to catalytic studies is the fact that this cavity is able to bind a metal centre, as confirmed structurally in [Cu(**2**)Gd($O_2NO)_3$][37] and [Cu(**1** − 2H)UCl_3(py)$_2$] (the pendant OH groups of ligand $\mathbf{1}^{2-}$ are deprotonated).[38] We have therefore looked at the effects of adding equimolar amounts (with respect to the [Cu(**3**)]) of copper(II), nickel(II), zinc(II) and palladium(II) acetate to the reaction mixture. The addition of $Zn(OAc)_2$ leads to extremely poor yield, but in contrast, the added $Cu(OAc)_2$ resulted in high yields when the solvent was



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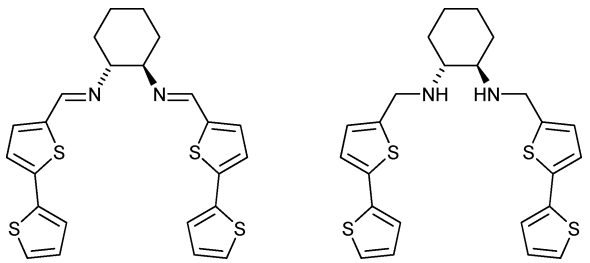
Scheme 3 Catalytic asymmetric Henry reaction of 4-nitrobenzaldehyde and nitromethane.

Table 1 Results for the catalytic asymmetric Henry reaction shown in Scheme 3

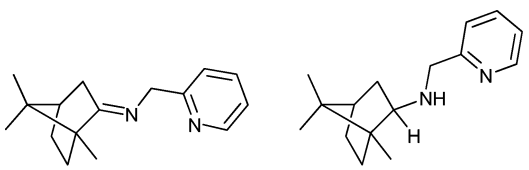
Complex	Added metal salt	Solvent	Temperature/K	Yield (%)[a]	ee (%)[b]
[Cu(**1**)]	None	EtOH	295 K	65	5
[Cu(**2**)]	None	EtOH	295 K	52	0
[Cu(**3**)]	None	EtOH	295 K	86	23
[Cu(**3**)]	None	THF	295 K	81	25
[Cu(**3**)]	None	CH_2Cl_2	295 K	80	15
[Cu(**3**)]	None	MeOH	295 K	40	23
[Cu(**3**)]	None	MeCN	295 K	56	9
[Cu(**3**)]	None	Toluene	295 K	41	48
[Cu(**3**)]	$Cu(OAc)_2$	EtOH	295 K	94	39
[Cu(**3**)]	$Cu(OAc)_2$	EtOH	273 K	82	44
[Cu(**3**)]	$Cu(OAc)_2$	THF	295 K	92	39
[Cu(**3**)]	$Pd(OAc)_2$	EtOH	295 K	65	30
[Cu(**3**)]	$Cu(OAc)_2$	Toluene	295 K	61	77
[Cu(**3**)]	$Zn(OAc)_2$	Toluene	295 K	<5	Not measured
[Cu(**3**)]	$Ni(OAc)_2$	Toluene	295 K	45	54

[a] Isolated yield after chromatographic purification. [b] Enantiomeric excess was determined by HPLC using a Chiralcel OD–H column.



5 **6**

Scheme 4 Ligands **5** and **6** from the work of Bandini *et al.*[20]



7 **8**

Scheme 5 Ligands **7** and **8** from the work of Blay *et al.*[21,22]

either EtOH or THF and the reaction carried out at room temperature. Moderate ee's were obtained (Table 1). In EtOH, an 82% yield and 44% ee were obtained even when the reaction was run at 273 K. The highest ee was obtained when the catalyst consisted of [Cu(**3**)]–$Cu(OAc)_2$ (1 : 1) and the solvent was toluene, and the yield was also enhanced with respect to the reaction catalysed only by [Cu(**3**)].

Starting from the crystallographically determined structure of [Cu(**3**)], we attempted to model a structure in which the *O*,*O*′,*O*″,*O*‴-cavity of [Cu(**3**)] binds a Cu(II) centre.[39] However, as expected, a severely distorted 4-coordinate environment is imposed upon the second copper(II) centre. The effect of the added metal ions is marked although we can only speculate as to the precise role. Assuming that the added copper(II) is bound by the catalyst, we propose that acetate ions are also involved, completing the coordination sphere. However, efforts to isolate a dimetallic complex from the reaction mixture have not been successful. Nonetheless, the observation that the addition of a second copper(II) centre enhances the performance of the catalyst is significant. These results complement the recent studies of Shibasaki and co-workers, who have shown that homo- and heterodimetallic (Ni_2, Cu–Sm) Schiff base complexes are efficient asymmetric catalysts for Mannich-type reactions.[40–42] These authors have also reported that trimetallic (Gd_3) complexes containing chiral ligands designed around a central cyclohexane ring bearing a pendant phosphine oxide are highly active enantioselective catalysts for ring-opening of *meso*-aziridines.[43]

Conclusions

The single-crystal structures of [Cu(**1**)(H_2O)] and [Cu(**3**)] are presented. In the former, the host–guest interactions and molecular packing contrast with those in [Cu(**2**)(H_2O)],[27] as a consequence of the differences in which the hydroxy and ethoxy substituents, respectively, in [Cu(**1**)] and [Cu(**2**)] interact with the H_2O molecule. We have investigated the use of copper(II) complexes of the chiral Schiff bases H_2**1** and H_2**2**, and of H_2**3** (the reduced analogue of H_2**1**) as catalysts for an asymmetric Henry reaction. [Cu(**1**)] and [Cu(**2**)] give poor yields and enantioselectivity, but with [Cu(**3**)], moderate to high yields and enantioselectivities were observed. The latter are solvent dependent, being highest in toluene rather than a polar solvent. Both yield and enantioselectivity are significantly enhanced when a second equivalent of $Cu(OAc)_2$ is added to the catalyst. We are currently attempting to establish this role for the metal ion by performing studies with less coordinating anions.

Ligand modification aimed towards further improvements of enantioselectivity in the Henry reaction and development of multimetallic catalysts based on reduced salen ligands are currently ongoing within our group.

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