Cu(II) homogeneous and heterogeneous catalysts for the asymmetric Henry reaction

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ABSTRACT

New Cu(II) complexes have been prepared and characterised *via* single crystal X-ray diffraction studies, EPR spectroscopy, elemental analysis and high resolution mass spectrometry. In all cases 1:2 (copper to ligand) stoichiometric complexes were isolated. The homogeneous Cu(II) complexes were tested for the asymmetric Henry reaction. Conversions in excess of 70% were obtained with enantioselectivities in the range 0–78%. Heterogeneous Cu(II) catalysts have been prepared. In these cases high conversions were obtained. However, after prolonged reaction time the main product observed was 1,3-dinitro-2-phenyl propane. The formation of this product can be curtailed by both decreasing the catalyst loading and employing shorter reaction times.

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1. Introduction

The Henry (nitroaldol) reaction is a fundamental carbon–carbon bond forming process in organic chemistry and is a key step in many syntheses [1,2]. In recent years the asymmetric variant of the Henry reaction has become a powerful method in the enantioselective preparation of carbon–carbon bonds. This transformation can be catalysed by Cu(II) complexes [3–14]. For example, Bandini et al. have investigated a series of C_2-symmetric oligothiophene Cu(II) systems [15]. Cu(II) bis-oxazolines have also shown promise in this area [10,16]. Blay et al. have successfully demonstrated the use of C_1-symmetric camphor derived ligands for the nitroaldol reaction of nitromethane and bromonitromethanes [17–20]. Cu(II) reagents based on (−)-sparteine are also active catalysts [21]. Recently, Constable demonstrated that Cu(II)-salen systems are effective with yields and enantioselectivities significantly enhanced with the addition of a further equivalent of Cu(OAc)$_2$ [22]. However, the Henry reaction is by no means limited to Cu(II), for example Zn(II) [23–25], Cr(III) [26,27], La(III) [28] and Co(II) [29] have all been shown to catalyse the reaction. The use of heterogeneous catalysts for this process remains limited. However, there have been successes with catalysts supported on PEG polymers, Wang type resins and dendrimers [30–32]. In this paper we have prepared five new Cu(II) complexes, all of which were characterised by single crystal X-ray diffraction. These complexes were tested for the asymmetric addition of nitromethane to benzaldehyde. Three classes of supported heterogeneous catalysts have been prepared; their characterisation (*via* solid-state NMR spectroscopy and EPR spectroscopy) is presented together with initial results for the asymmetric Henry reaction.

2. Experimental

2.1. General procedures

^{1}H and ^{13}C{^{1}H} NMR spectra were recorded on a Bruker 300 or 250 MHz spectrometer, and referenced to residual solvent peaks (CDCl$_3$). Coupling constants are given in Hertz. Elemental analysis was performed by Mr. A.K. Carver at the Department of Chemistry, University of Bath. (1*R*,2*R*)-1,2-Diaminocyclohexane was resolved from the commercially available *trans*-1,2-diaminocyclohexane by the method of Jacobsen and co-workers [33]. ICP analysis was performed by Medac Ltd. Nanoporous carbon was purchased from Aldrich (<50 nm particle size, surface area > 100 m^2 g^{-1}) and used as received.

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2.2. X-ray crystallography

Data were collected on a Nonius Kappa CCD diffractometer using Mo-Kα radiation ($\lambda = 0.71073$ Å) at a temperature of 150(2) K, except for Cu(**4**)$_2 \cdot$(OTf)$_2$ which was collected on a Xcalibur, Atlas diffractometer using CuKα radiation ($\lambda = 1.54184$ Å) at 100(2) K. All structures were solved by direct methods and refined on all F^2 data using the SHELXL-97 suite of programs. All hydrogen atoms were included in idealised positions and refined using the riding model. Refinements were generally straightforward with the following exceptions and points of note. For Cu(**2**)$_2 \cdot$(OTf)$_2$ excellent convergence was obtained once pseudo-merohedral twinning (47%) about the $-1\,0\,1$ direct lattice direction had been addressed. The unit cell metrics in concert with the extent and nature of the twinning suggested higher symmetry (orthorhombic 'C', or monoclinic 'C') initially, neither of which produced a credible model. For Cu(**2**)$_2 \cdot$(OTf)$_2$ the ADPs for C(25) are slightly less isotropic than desirable, but efforts to model disorder in this region of the electron density map afforded no improvement in convergence. Despite copious recrystallisation efforts only small crystals (0.05 mm × 0.05 mm × 0.01 mm) for Cu(**4**)$_2 \cdot$(OTf)$_2$ were obtained, due to this weak diffraction the data was truncated to $\theta = 62.26$ (CuKα). Nonetheless, the structure is unambiguous. For the Cu(**5**)$_2^{2+}$ cation the copper centre was modelled over two sites in a 80:20 ratio. Multi-scan absorption corrections were applied to the data on merit.

2.3. Solid-state NMR

Solid-state NMR spectra were recorded at the EPSRC national solid-state NMR service centre (Durham University) on a Varian VNMRS 400 MHz spectrometer (100.562 MHz for ^{13}C), using the cross-polarization pulse sequence (contact time 3.0 ms and recycle delay 1.0 s), with TPPM decoupling. A spinning rate of 10.0 kHz was employed.

2.4. EPR

All the measurements were performed using a Bruker EMX spectrometer at X-band ($\sim$9.4 GHz) and K-band ($\sim$24.0 GHz) at room temperature and at 120 K. The samples were measured as powders at 290 and 120 K, fluid solutions at 290 K and frozen solution at 120 K. The simulations of the spectra were performed using Bruker XSophe computer simulation software (version 1.1.4).

2.5. Ligand preparation and characterisation

The ligands were prepared *via* standard procedures [34,35], a typical procedure for **3** and **4** are given in supporting information.

2.6. Complex preparation and characterisation

A typical procedure for Cu(**1**)$_2 \cdot$(OTf)$_2$. **1** (0.82 g, 2.8 mmol) was dissolved in MeOH (10 mL) to which Cu(OTf)$_2$ (0.5 g, 1.4 mmol) was added. This was stirred for 1 h and the solution removed in vacuo. The resulting blue powder was recrystallised from MeOH and Et$_2$O at $-20\,^\circ$C and a crop of deep blue crystals was obtained after 2 days. Cu(**1**)$_2 \cdot$(OTf)$_2$. HR-ESI Calc. for [M^{2+}] 145.5800 found 145.5807. Calc. for C$_{14}$H$_{28}$CuF$_6$N$_4$O$_6$S$_2$ C, 28.47; H, 4.75; N, 9.49. Found C, 28.2; H, 4.97; N, 9.12. FT-IR (solid cm^{-1}) 3267w, 2935w, 1603m, 1589m 1494m 1468m, 1289s, 1239s, 1154m 1118m, 919m, 757s, 635s. C$_{28}$H$_{56}$Cu$_2$F$_{12}$N$_8$O$_{12}$S$_4$, $M = 1180.13$, 0.40 mm × 0.30 mm × 0.25 mm, triclinic, $P1$, $a = 8.6140(1)$ Å, $b = 11.6740(2)$ Å, $c = 11.7340(2)$ Å, $\alpha = 81.757(1)^\circ$, $\beta = 87.113(1)^\circ$, $\gamma = 89.344(1)^\circ$, $V = 1166.29(3)$ Å^3, $Z = 1$, $D_c = 1.680$ g/cm^3, $F_{000} = 606$, $2\theta_{max} = 55.0^\circ$, 22,337 reflections collected, 10,000 unique

($R_{int} = 0.0313$). Final $GooF = 1.052$, $R_1 = 0.0263$, $wR_2 = 0.0614$, R indices based on 9626 reflections with $I > 2\sigma$ (refinement on F^2), 595 parameters, 3 restraints. $\mu = 1.201$ mm^{-1}. Absolute structure parameter = $-0.006(5)$.

Cu(**2**)$_2 \cdot$(OTf)$_2$ HR-ESI Calc. for [M^{2+}] 325.6739 found 325.6736. Calc. for C$_{42}$H$_{52}$CuF$_6$N$_4$O$_6$S$_2$ C, 53.07; H, 5.51; N, 5.89. Found C, 52.3; H, 5.44; N, 5.74. FT-IR (solid cm^{-1}) 3224w, 3156w, 2948w, 1497w, 1455m, 1287m, 1241s, 1147s, 1026s, 987m, 761m, 634 s. C$_{42}$H$_{52}$CuF$_6$N$_4$O$_6$S$_2$, $M = 950.54$, 0.35 mm × 0.20 mm × 0.10 mm, monoclinic, $P2_1$, $a = 11.7300(1)$ Å, $b = 35.5410(4)$ Å, $c = 11.7290(1)$ Å, $\beta = 114.6240(1)^\circ$, $V = 4445.10(7)$ Å^3, $Z = 4$, $D_c = 1.420$ g/cm^3, $F_{000} = 1980$, $2\theta_{max} = 54.9^\circ$, 35572 reflections collected, 35,590 unique. Final $GooF = 1.186$, $R_1 = 0.0467$, $wR_2 = 0.1288$, R indices based on 33,459 reflections with $I > 2\sigma$ (refinement on F^2), 1100 parameters, 1 restraint. $\mu = 0.661$ mm^{-1}. Absolute structure parameter = $-0.009(9)$.

Cu(**3**)$_2 \cdot$(OTf)$_2$ HR-ESI Calc. for [M^{2+}] 385.6950, found 385.6950. Calc. for C$_{46}$H$_{60}$CuF$_6$N$_4$O$_{10}$S$_2$ C, 51.60; H, 5.65; N, 5.23. Found C, 51.5; H, 5.63; N, 5.21. FT-IR (solid cm^{-1}) 3327w, 3225w, 2944w, 1595m 1454m, 1290s, 1241s, 1221s, 1158s, 1025s, 758m, 706m, 631s. C$_{46}$H$_{60}$CuF$_6$N$_4$O$_{10}$S$_2$, $M = 1070.64$, 0.10 mm × 0.10 mm × 0.10 mm, monoclinic, $P2_1$, $a = 11.5320(5)$ Å, $b = 18.6300(1)$ Å, $c = 11.8630(6)$ Å, $\beta = 102.643(3)^\circ$, $V = 2486.9(2)$ Å^3, $Z = 2$, $D_c = 1.430$ g/cm^3, $F_{000} = 1118$, $2\theta_{max} = 50.0^\circ$, 28,133 reflections collected, 8616 unique ($R_{int} = 0.1396$). Final $GooF = 1.029$, $R_1 = 0.0637$, $wR_2 = 0.1220$, R indices based on 5199 reflections with $I > 2\sigma$ (refinement on F^2), 681 parameters, 1 restraint. $\mu = 0.605$ mm^{-1}. Absolute structure parameter = $-0.008(18)$.

Cu(**4**)$_2 \cdot$(OTf)$_2$ Calc. for C$_{46}$H$_{60}$CuF$_6$N$_4$O$_6$S$_2$ C, 54.88; H, 6.01; N, 5.57. Found C, 53.5; H, 5.88; N, 5.49. FT-IR (solid cm^{-1}) 3256w, 2945w, 1494w, 1459w, 1284s, 1247s, 1231s, 1163m, 1024s, 921m, 751m, 742m, 637s. C$_{93}$H$_{124}$Cu$_2$F$_{12}$N$_8$O$_{13}$S$_4$, $M = 2045.32$, 0.05 mm × 0.05 mm × 0.01 mm, monoclinic, $P2_1$, $a = 11.4238(7)$ Å, $b = 32.3577(8)$ Å, $c = 13.0790(4)$ Å, $\beta = 96.545(4)^\circ$, $V = 4803.1(3)$ Å^3, $Z = 2$, $D_c = 1.414$ g/cm^3, $F_{000} = 2144$, CuKα radiation, $\lambda = 1.54184$ Å, $2\theta_{max} = 124.5^\circ$, 22,418 reflections collected, 10,864 unique ($R_{int} = 0.0735$). Final $GooF = 0.878$, $R_1 = 0.0466$, $wR_2 = 0.0789$, R indices based on 7323 reflections with $I > 2\sigma$ (refinement on F^2), 1194 parameters, 1 restraint. $\mu = 2.106$ mm^{-1}. Absolute structure parameter = 0.027(19).

Cu(**5**)$_2 \cdot$(OTf)$_2 \cdot$H$_2$O HR-ESI Calc. for [M^{2+}] 159.5956; found 159.5954. Calc. for C$_{16}$H$_{34}$CuF$_6$N$_4$O$_7$S$_2$ C, 30.21; H, 5.39; N, 8.81. Found C, 30.2; H, 5.38; N, 8.75. FT-IR (solid cm^{-1}) 3416w, 3245w, 2963w, 1665w, 1604w, 1461w, 1250s, 1226m, 1027s, 943m, 760m, 632s. C$_{16}$H$_{34}$CuF$_6$N$_4$O$_7$S$_2$, $M = 636.13$, 0.40 mm × 0.15 mm × 0.10 mm, tetragonal, $P4_12_12$, $a = b = 12.6100(1)$ Å, $c = 16.2480(2)$ Å, $V = 2583.63(4)$ Å^3, $Z = 4$, $D_c = 1.635$ g/cm^3, $F_{000} = 1316$, $2\theta_{max} = 54.9^\circ$, 51,652 reflections collected, 2957 unique ($R_{int} = 0.0434$). Final $GooF = 1.075$, $R_1 = 0.0226$, $wR_2 = 0.0573$, R indices based on 2885 reflections with $I > 2\sigma$ (refinement on F^2), 169 parameters, 3 restraints. $\mu = 1.094$ mm^{-1}. Absolute structure parameter = $-0.013(10)$.

2.7. Synthesis of heterogeneous catalysts

To prepare the amine grafted material, silica (60 Å Davisil grade) was initially reacted with (MeO)$_3$Si(CH$_2$)$_3$NH$_2$ [36,37].

A Amine functionalised silica (10 g, 10 mmol loading of NH$_2$) was suspended in CH$_2$Cl$_2$ (100 mL), and terephthalaldehyde (1.34 g, 10 mmol) added. The mixture was stirred at room temperature for 2 h before the silica material was collected and washed with CH$_2$Cl$_2$ (3 × 50 mL) and dried. C, 8.60; H, 1.39; N, 1.27.

B The previously synthesised silica material (**A**) (3.9 g) was suspended in CH$_2$Cl$_2$ (50 mL) and (R,R)-1,2-diaminocyclohexane (0.4 g, 3.9 mmol) added. The mixture was stirred at room temperature for

4 h before the silica material was collected and washed with CH_2Cl_2 (3× 50 mL) and dried. C, 8.78; H, 1.90; N, 2.33.

C The previously synthesised silica material (**B**) (1.5 g) was suspended in CH_2Cl_2 (50 mL) and benzaldehyde (0.15 mL, 1.5 mmol) added. The mixture was stirred at room temperature for 4 h before the silica material was collected and washed with CH_2Cl_2 (3× 50 mL) and dried, C, 8.74; H, 1.73; N, 1.78. Copper catalysts: the previously synthesised silica material (**C**) (1.0 g) and $Cu(OTf)_2$ (0.5 g, 1.5 mmol) were placed in a flask under argon, and methanol (40 mL) added. The mixture was stirred at room temperature for 1 h before the silica material was collected. The product was washed with methanol (3× 50 mL) until the washings were clear and dried. C, 6.10; H, 1.36; N, 1.23, Cu 0.28%.

D Analogous to **C** except *o*-OMe-benzaldehyde (0.18 mL, 1.5 mmol) was added. C, 8.63; H, 1.55; N, 1.67. Copper catalyst: analogous method as detailed above. C, 6.43; H, 1.30; N, 1.24.

E Analogous to **C** except *o*-tolualdehyde (0.17 mL, 1.5 mmol) was added. C, 8.86; H, 1.66; N, 1.79. Copper catalyst: Analogous method as detailed above C, 6.11; H, 1.33; N, 1.18.

2.8. Preparation of Cu-exchanged zeolite Y

Zeolite HY (10 g) was stirred with a solution of $Cu(OAc)_2$ (1.57 g, 7.86 mmol) in distilled water (30 mL) for 24 h at room temperature. The zeolite material was collected by vacuum filtration, dried under vacuum at 100 °C and calcined at 550 °C, pXRD of the calcined material was analogous to that of pure zeolite HY. Cu-exchanged zeolite Y (0.36 g, 0.090 mmol Cu, based on ICP results of 1.6 wt% Cu in the sample) was placed under argon, and to this a solution of chiral ligand (0.075 mmol) in CH_2Cl_2 (10 mL) was added. After stirring at room temperature for 3 h, benzaldehyde (0.1 mL, 1.0 mmol), nitromethane (0.55 mL, 10 mmol) and triethylamine (35 µl, 0.25 mmol) were added, and the mixture stirred at room temperature for a pre-determined time.

2.9. Preparation of Cu on carbon catalysts [38]

Nanoporous carbon (500 mg) was suspended in methanol (10 mL) to which the copper complex (2.35×10^{-5} mol) was added. This was stirred overnight, filtered, washed with methanol (2× 20 mL) and dried in vacuo.

2.10. Typical catalytic procedure

Under argon EtOH (10 mL) was added to a Schlenk flask, to which the Cu(II) homogeneous catalyst was added (0.05 mmol) or the desired amount of heterogeneous catalyst and the solution stirred. Benzaldehyde (0.1 mL, 1.0 mmol), nitromethane (0.55 mL, 10 mmol) and NEt_3 (35 µL, 0.25 mmol) were added and the solution stirred for the appropriate amount of time. After the desired time the reaction was filtered through a plug of silica and the solvents were removed in vacuo. ^1H NMR spectroscopy was used to determine the conversion by analysis of the 1H integral of PhC**H**O at 9.94 ppm to the 1H integral of PhC**H**(OH)CH_2NO_2 at 5.45 ppm. For the heterogeneous catalysts a 1H quintet {Ph(C**H**)(CH_2NO_2)$_2$} at 4.25 ppm and a 1H doublet at 7.90 ppm for {PhC**H**=$CHNO_2$} were accounted for in the selectivity measurements. The enantiomeric excess was determined by HPLC using an Agilent Compact 1120 LC with UV detection (254 nm). A flow rate of IPA:hexane (1:9) at 1 mL/min was used with a Lux Cellolose-1 column, the retention times were 16 and 19 min for the two enantiomers.

3. Results and discussion

3.1. Preparation and characterisation of Cu(II) complexes

Ligands **1**–**4** were prepared *via* standard literature procedures. Ligands of this type have shown promise for the asymmetric Henry reaction [22]. Ligand **5** was purchased from Aldrich. All complexes prepared are shown in Scheme 1.

All complexes were characterised by single crystal X-ray diffraction, see Fig. 1 for the molecular structure of the Cu(**2**)$_2$$^{2+}$ cation. This paper reports the crystallographic characterisation of all the Cu(II) complexes. Cu(**1**)$_2$·(OTf)$_2$ crystallises in the triclinic space group $P1$ and contains two copper centres in the asymmetric unit. The copper centre is coordinated by two diamine ligands and one weakly coordinated OTf^- counter-ion giving the copper centre a coordination number of five. The Cu–N distances of approximately 2.0 Å are analogous to literature precedent [39–42]. Cu(**2**)$_2$·(OTf)$_2$ crystallises in the monoclinic space group $P2_1$, with two Cu(II) centres in the asymmetric unit. Two diamine moieties coordinated to each Cu(II) centre and no Cu–OTf interactions are observed. The copper centres are in a highly distorted square planar geometry, as exemplified by the range of N–Cu(1)–N angles present in the structure {*cis* interactions 85.25(16)–102.64(18)° and for *trans* 149.78(17)–152.11(16)°}. Cu(**3**)$_2$·(OTf)$_2$ crystallises in the monoclinic space group $P2_1$. In this case the Cu(II) centre is best described has having a slightly distorted square planar geometry. Cu(**4**)$_2$·(OTf)$_2$ crystallises in the monoclinic space group $P2_1$ with two Cu(II) centres in the asymmetric unit. The Cu(II) centre again is pseudo square planar, see supporting information for selected bond distances and angles. For both Cu(**3**)$_2$·(OTf)$_2$ and Cu(**4**)$_2$·(OTf)$_2$ two diamine ligands are coordinated to the Cu(II) centre together with a weakly coordinating OTf^- counter-ion.

There are significant differences in the coordination geometries between Cu(**2**)$_2$·(OTf)$_2$ and either Cu(**3**)$_2$·(OTf)$_2$ or Cu(**4**)$_2$·(OTf)$_2$. These are manifested by analysis of the Cu–NH–CH_2–C_{Ar} torsion angles. For Cu(**2**)$_2$·(OTf)$_2$ these are in the range 47.6–65.7°, however for Cu(**3**)$_2$·(OTf)$_2$ the analogous angles are 85.9–169.3° and for Cu(**4**)$_2$·(OTf)$_2$ 59.7–177.3°. There is also a significant difference between the angle of the planes formed from N(1)–Cu(1)–N(2) and N(3)–Cu(1)–N(4) which are close to parallel (*i.e.* 180°) for Cu(**3**)$_2$·(OTf)$_2$ and Cu(**4**)$_2$·(OTf)$_2$. However, for Cu(**2**)$_2$·(OTf)$_2$ the analogous angle is 139°. Cu(**5**)$_2$·(OTf)$_2$·H_2O crystallised in the tetragonal space group $P4_12_12$, Fig. 1. The copper centre is best
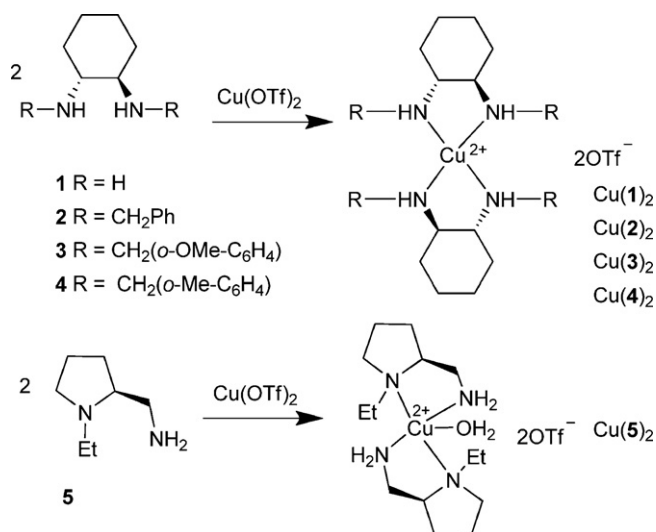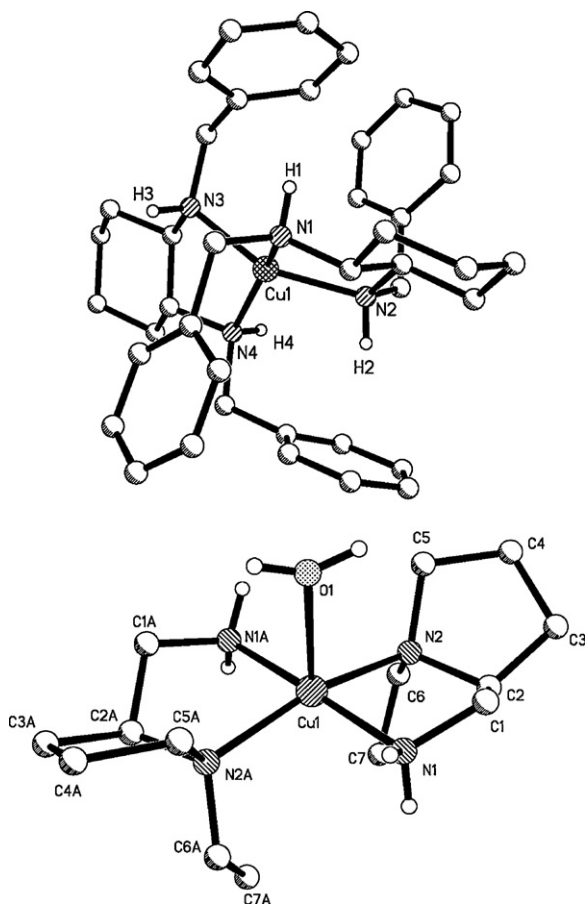

Scheme 1. Complexes prepared in this study.

Fig. 1. Molecular structures of Cu(**2**)$_2^{2+}$ (top) and Cu(**5**)$_2^{2+}$·H$_2$O cation (bottom), the triflate counter-ions and all hydrogen atoms except those bound to nitrogen atoms and water have been removed for clarity. Atoms labelled with a suffix A are generated by the $-x+1, -y+1, -z+\frac{1}{2}$ symmetry operation.

Table 1
Catalytic results for the homogeneous catalysts.

Catalyst[a]	Time/h	Equiv. NEt$_3$[b]	Conv.[c]	ee[d]
Cu(**1**)$_2$·(OTf)$_2$	6	0.25	68	0
Cu(**2**)$_2$·(OTf)$_2$	6	0.25	45	60 (S)
Cu(**3**)$_2$·(OTf)$_2$	4	0.5	75	43 (S)
Cu(**3**)$_2$·(OTf)$_2$	6	0.25	59	68 (S)
Cu(**3**)$_2$·(OTf)$_2$	6	0.13	20	72 (S)
Cu(**4**)$_2$·(OTf)$_2$	6	0.25	26	78 (S)
Cu(**5**)$_2$·(OTf)$_2$	4	0.5	76	36 (R)

[a] The catalyst:benzaldehyde:nitromethane molar ratio was 0.05:1:10.
[b] Equivalent (with respect to benzaldehyde).
[c] Conversion as determined by ^{1}H NMR spectroscopic analysis.
[d] Determined by chiral HPLC, the absolute configuration was determined by optical rotation data.

described as square based pyramidal. In this case a molecule of water is coordinated to the metal centre with a Cu(1)–O(1) distance of 2.3076(15) Å. The complexes were also analysed *via* mass spectrometry and IR spectroscopy. Mass spectrometry afforded the parent M^{2+} ion, noteworthy for Cu(**1**)$_2$·(OTf)$_2$ a peak at 440.1128 (Calc. 440.1130) was also observed indicating that one OTf counter-ion maybe coordinated in solution. To further characterise these materials EPR spectroscopy was performed on Cu(**2**)$_2$·(OTf)$_2$ and Cu(**5**)$_2$·(OTf)$_2$·H$_2$O (see supporting information for further details and for a table of g and A values). For Cu(**5**)$_2$·(OTf)$_2$·H$_2$O the simulation of the frozen solution spectrum at X-band at 130 K gave an axial set of g values and A values with $g_\perp = 2.05, g_\parallel = 2.20$ and $A_\perp = 52.6 \times 10^{-4}$ cm^{-1}, $A_\parallel = 187.6 \times 10^{-4}$ cm^{-1}, which are in agreement with literature precedent for complexes with analogous structural motifs as those described herein [43–46]. For Cu(**2**)$_2$·(OTf)$_2$ simulation of the frozen solution spectrum at X-band at 130 K gave an axial set of g values and A values with $g_\perp = 2.05, g_\parallel = 2.20$ and $A_\perp = 23.9 \times 10^{-4}$ cm^{-1}, $A_\parallel = 180.8 \times 10^{-4}$ cm^{-1}. For both complexes the analysis was relatively complex, with evidence of multiple Cu(II) sites present, which could arise from coordination of the triflate anion or solvent molecules. For Cu(**2**)$_2$·(OTf)$_2$ there was also evidence for dimer formation in solution.

3.2. Homogeneous catalysis

The catalytic activity for the asymmetric nitroaldol coupling of nitromethane and benzaldehyde was investigated for the five cop-

per catalysts. The procedure was also attempted with free ligand **4** (without base) as there are examples of organocatalysed Henry reactions [47]. In this case after 6 h a 40% conversion was obtained but it failed to induce any enantioselectivity in the product. All the Cu(II) catalysed transformations were performed using 1 mmol of benzaldehyde, 10 mmol of nitromethane, 0.05 mmol of catalyst and 0.5, 0.25, 0.13 mmol of the promoter triethyl amine, Table 1. The conversions were determined *via* ^{1}H NMR spectroscopy and the enantiomeric excess from HPLC. Cu(**1**)$_2$·(OTf)$_2$ was relatively active for the Henry reaction but failed to induce any selectivity in the product [15]. However, Cu(**2**–**5**)$_2$·(OTf)$_2$ were successful in conferring enantioselectivity into the process, with the highest ee being 78% for Cu(**4**)$_2$·(OTf)$_2$. It is observed that increasing the steric bulk of the substituent on the aromatic ring (H to Me to OMe) has the effect of increasing the enantioselectivity in the product. Decreasing the amount of the NEt$_3$ promoter increased the selectivity, but at the expense of conversion. In this case it was seen that without NEt$_3$ no activity was observed. During the catalysis itself the counter-ion is presumably no longer coordinated to the copper centre to facilitate the coordination of benzaldehyde and nitromethane to allow the catalysis to proceed.

3.3. Preparation, characterisation and catalysis of the heterogeneous systems

Various supported systems have been utilised and are described herein for the asymmetric Henry reaction. Specifically the reaction we are studying is the addition of benzaldehyde to nitromethane [30–32]. Important to this study is that silica and zeolites materials have not been used extensively as supports for this reaction, therefore we attempted to heterogenize the ligands described herein to these supports [48,49]. The heterogeneous catalysts were prepared as shown in Fig. 2. ^{13}C{^{1}H} CP/MAS solid-state NMR spectroscopic analyses are in agreement with the desired structures, Fig. 3 [36]. For example **A** has resonances at 9, 23, 58 and 63 ppm for the CH$_2$'s of the propyl tether and unreacted OMe [36]; the aromatic peaks are centred at 127 and 138 ppm, the imine carbon is seen at 161 ppm and the carbonyl at 194 ppm. After reaction with (1R,2R)-1,2-diaminocyclohexane new resonances at 25, 33 and 43 ppm are observed for the cyclohexane ring, and as expected there is a disappearance of the CHO peak observed in **A**. For **C**, **D** and **E** there is an increase in the intensity of the aromatic resonances compared to **B** which would be expected after the reaction with the benzaldehyde derivative. For **D** there is a new peak at 54 ppm for the OMe group and additional intensity for the peak at 160 ppm arising from the aromatic carbon attached to the methoxy group. For **E** there is a new resonance at 17 ppm consistent with the presence of the methyl substituent and an increase in intensity of the resonance at 138 ppm from the aromatic carbon bound to the methyl group. To further characterise these materials the solid Cu^{2+} catalysts, where R = OMe or Me, were analysed *via* EPR spectroscopy. The simulation
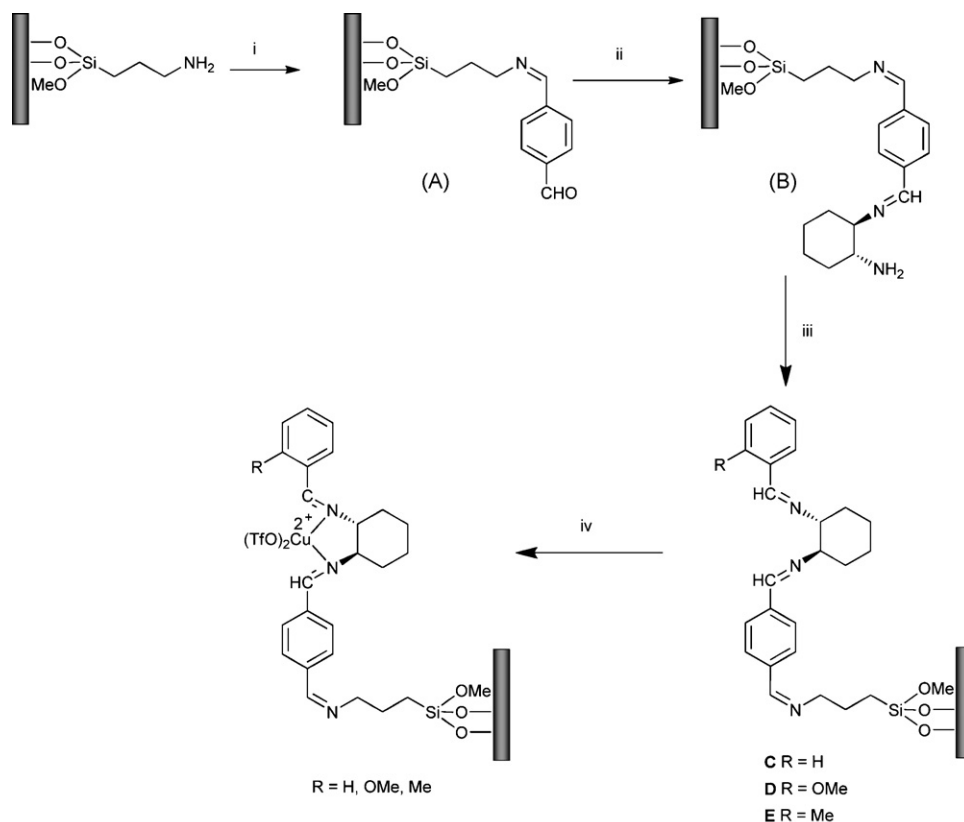
Fig. 2. Preparation of the heterogeneous Cu(II) catalysts. (i) 1,4-Benzenedicarboxaldehyde/MeOH, (ii) (1*R*,2*R*)-diaminocyclohexane, (iii) benzaldehyde, 2-methylbenzaldehyde or 2-methoxybenzaldehyde/MeOH, (iv) Cu(OTf)$_2$/MeOH.

of the powder spectrum of samples at *X*-band, at 290 and 130 K, are consistent with the presence of Cu(II) in the material. Both heterogeneous catalysts have the same parameters $g_\perp = 2.05, g_{||} = 2.25$ and $A_\perp = 23.0 \times 10^{-4}\,cm^{-1}, A_{||} = 191.2 \times 10^{-4}\,cm^{-1}$. These are analogous to Cu(II)-imine systems in the literature supporting the structures proposed in Fig. 2 [46]. These values are also analogous to the homogeneous catalysts prepared in this study.

The solid-supported systems were tested for the Henry reaction (1:10:0.25 molar ratio of benzaldehyde:nitromethane:triethylamine) using 200 mg of the supported system and for a period of 72 h.

Good conversions *ca.* 100% were observed, as there was no evidence of benzaldehyde in the ^{1}H NMR spectrum. However, the major product formed in the reaction was 1,3-dinitro-2-phenyl propane as opposed to the desired nitroaldol species, β-nitrostyrene was also observed [50–53]. 1,3-Dinitro alkanes have been shown to be key building blocks in the synthesis of HIV-protease inhibitors and other biologically important interme-

diates [54]. These alkanes have been shown to be produced from heterogeneous primary amine/tertiary amine catalysts [50]. Significantly, acid surfaces have been shown to enhance the activity *via* a cooperative mechanism involving free amines on the surface and potentially by activating the intermediate β-nitrostyrene to attack by nitromethane [52]. This is presumably a possible explanation for the observation of this by-product in this case, as the support is acidic and in these systems there are potentially free amine (–NH$_2$) sites on the surface remaining from unreacted moieties. Although not the main thrust of this work it should be noted that the formation of 1,3-dinitro alkanes is typically performed at elevated temperatures [51]. In an attempt to reduce the undesired side-reaction 100 and 200 mg of catalyst were used for 24 h, Table 2. Noteworthy, a switch in enantioselectivity on going from the homogeneous to the heterogeneous systems was observed. Bandini et al. observed (with the same absolute stereochemistry in the backbone) a change in selectivity on going from an amine to the analogous imine with his oligothiophene Cu(II) systems [15]. We suggest that this is also the case here as the silica supported heterogeneous cat-
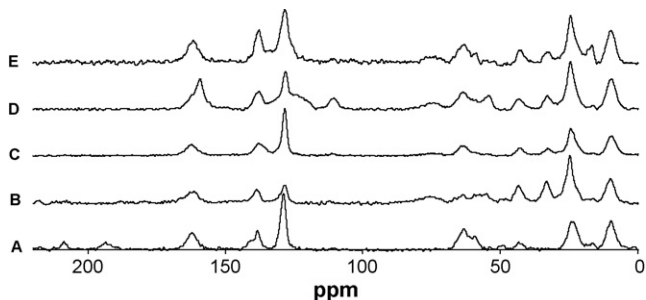

Fig. 3. ^{13}C{^{1}H} CP/MAS solid-state NMR spectroscopic analysis for the heterogeneous supported systems. See Fig. 2 for the structures of **A**, **B**, **C**, **D**, **E**.

Table 2
Catalytic results for the heterogeneous systems.

Catalyst	Time/h	Loading/mg[a]	Conv.[b]	Selectivity[b]	ee[c]
Cu–H	24	200	99	64	5 (R)
Cu–H	24	100	95	78	10 (R)
Cu–OMe	24	200	86	70	31 (R)
Cu–OMe	24	100	80	82	22 (R)
Cu–Me	24	200	99	72	34 (R)
Cu–Me	24	100	76	73	25 (R)

[a] The benzaldehyde:nitromethane:NEt$_3$ molar ratio was 1:10:0.25.
[b] Conversion/selectivity as determined by ^{1}H NMR analysis.
[c] Determined by chiral HPLC, the absolute stereochemistry was determined by optical rotation data.

Table 3
Catalytic results for the zeolite heterogeneous catalysts.

Catalyst[a]	Time/h	Conv.[b]	Selectivity[b]	ee[c]
Cu–H	24	71	91	44 (S)
Cu–OMe	24	47	81	22 (S)
Cu–Me	24	49	100	42 (S)

[a] The catalyst:benzaldehyde:nitromethane molar ratio was 0.05:1:10, 35 μL of NEt$_3$ used loading of Cu-exchanged zeolite HY 0.36 g.
[b] Conversion/selectivity as determined by ^{1}H NMR spectroscopic analysis.
[c] Determined by chiral HPLC, the absolute stereochemistry was determined by optical rotation data.

Table 4
Catalytic results for the carbon heterogeneous catalysts.

Catalyst[a]	Equiv. NEt$_3$[b]	Time/h	Conv.[b]	Selectivity[b]	ee[c]
Cu(**2**)$_2^{2+}$ on C	0.25	48	96	94	48 (S)
Cu(**3**)$_2^{2+}$ on C	0.25	48	95	94	47 (S)
2nd use	0.25	48	80	94	33 (S)
Cu(**3**)$_2^{2+}$ on C	0.13	48	91	98	61 (S)
2nd use	0.13	48	73	100	32 (S)

[a] The benzaldehyde:nitromethane:NEt$_3$ molar ratio was 1:10:0.25, 100 mg of heterogeneous catalyst used.
[b] Conversion/selectivity as determined by ^{1}H NMR spectroscopic analysis.
[c] Determined by chiral HPLC, the absolute stereochemistry was determined by optical rotation data.

alysts are imines whereas the homogeneous are amines [15]. There is also an increase in selectivity on reducing the reaction time and catalyst loading and modest enantioselectivites were observed. The residue from the Cu–Me catalyst with 200 mg for 24 h contained 14 ppm of Cu (from ICP measurements) in the product, indicating that minimal leaching had occurred. Attempts to prepare and isolate the imine variants of the complexes proved unsuccessful. In fact when the imine version of **2** was reacted with Cu(OTf)$_2$ crystals of Cu(**1**)$_2$·(OTf)$_2$ were isolated, implying that the imine functionality is not stable under these conditions in the homogeneous phase. This coupled with the low ee's and selectivity of these heterogenised catalysts led us to investigate the possibility of using other supports.

It has been demonstrated that Cu-exchanged zeolite HY with bis(oxazoline) ligands are effective for the carbonyl-ene reaction [55]. In an attempt to improve the selectivity in our Henry system towards the nitroaldol product (as there would be no free amine on the surface to aid the formation of the 1,3-dinitro alkanes), the diamine ligands were heterogenised on copper exchanged zeolite HY, Table 3 [55]. Compared to the silica supported system there was a slight increase in both selectivity (in this case the major byproduct was β-nitrostyrene) and enantioselectivity. The residue from the Cu–Me catalyst contained 12 ppm of Cu in the product, implying the catalysis is heterogeneous. When the silica and zeolite systems were reacted for 72 h, near quantitative conversions were observed, although the selectivities decreased significantly.

It has been shown that simple catalysts can be anchored to carbon supports *via* ionic interactions [38]. Carbon was chosen as this support has no Brønsted acid sites to facilitate the production of the side products. The catalysts were prepared by stirring a slurry of carbon with the copper complexes in methanol. High conversions and selectivities were obtained and good enantioselectivities, even with low amounts of NEt$_3$, Table 4. On reuse of the catalyst, unfortunately there was a significant reduction in both activity and ee, implying that theses species may not be truly heterogeneous.

4. Conclusions

Five Cu(II) homogeneous complexes have been prepared and characterised *via* single crystal X-ray diffraction studies. The complexes were shown to be active for the asymmetric coupling of nitromethane and benzaldehyde. Heterogeneous copper containing catalysts were also prepared which also showed good conversions but modest selectivities. Future work is aimed at improving the selectivity of the heterogeneous systems and at developing base free catalysed processes.

Supporting information

Full experimental details (EPR, synthesis procedures and representative NMRs) and crystal data in the .cif format are available. CCDC numbers 751,962–751,966 contain the supplementary crystallographic data for this paper and can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgments

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molcata.2010.03.013.

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