

# Enantioselective catalysts for the Henry reaction: fine-tuning the catalytic components†

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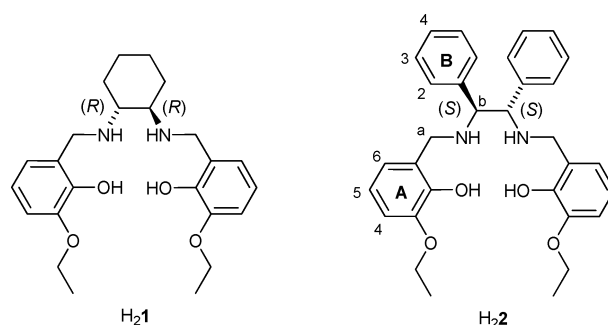
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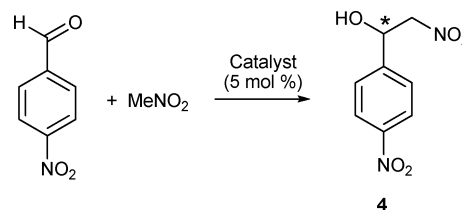
Catalysts for the asymmetric Henry reaction involving 1,6-bis(3-ethoxy-2-hydroxyphenyl)-(3*S*,4*S*)-(–)-diphenyl-2,5-diazaheptane (**H<sub>2</sub>2**) and copper salts have been investigated. Conditions for the conversion of 4-nitrobenzaldehyde to 2-nitro-1-(4-nitrophenyl)ethanol by reaction with nitromethane have been optimized (5 mol% **H<sub>2</sub>2**, 10 mol% CuI, THF, 295 K and 2 hours or 273 K and 12 hours) resulting in 99% yield and 90–92% ee. These catalytic conditions are effective for other aromatic aldehydes containing electron-withdrawing substituents, and for pyridine carbaldehydes; representative aliphatic aldehydes were converted to the respective β-hydroxynitro derivatives with good enantioselectivities, and in moderate yields. These catalytic conditions were found to be ineffective for simple aromatic aldehydes or those containing electron-releasing substituents.

## Introduction

In synthetic chemistry, the Henry (or nitroaldol) reaction is becoming an increasingly important carbon–carbon bond forming reaction,<sup>1–3</sup> and the β-hydroxynitro compounds so formed find application in the synthesis of key intermediates such as chiral β-amino alcohols and α-hydroxyl carboxylic acids.<sup>3–6</sup> Current interest in enantioselective and diastereoselective Henry reactions<sup>7–13</sup> has led to the development of chiral catalysts containing copper,<sup>10,14–37</sup> cobalt,<sup>38,39</sup> chromium<sup>40–42</sup> and zinc,<sup>43</sup> as well as heterodimetallic complexes.<sup>11,44</sup> Schiff base ligands are central to many of these catalysts, the preparation of these compounds from amine and carbonyl precursors being facile. In developing new catalysts for the asymmetric Henry reaction, it is advantageous for catalysis to be carried out under mild (ideally ambient) reaction conditions. We have recently described catalytic studies of the asymmetric Henry reaction using copper(II) complexes of the chiral Schiff bases 1,6-bis(2-hydroxyphenyl)-(3*R*,4*R*)-(–)-cyclohexane-1,2-diyl-2,5-diazaheptane-1,5-diene, 1,6-bis(3-ethoxy-2-hydroxyphenyl)-(3*R*,4*R*)-(–)-cyclohexane-1,2-diyl-2,5-diazaheptane-1,5-diene and the reduced analogue of the latter, **H<sub>2</sub>1** (Scheme 1).<sup>34</sup> Of these, the most promising catalyst was [Cu(**1**)] which produced moderate to high yields and enantioselectivities which were optimal when reactions were carried out in toluene rather than a polar solvent. We observed that both the yield and the enantioselectivity were enhanced when a second equivalent of Cu(OAc)<sub>2</sub> was added to the catalyst. We report here a detailed study of the use of copper complexes of the reduced Schiff base ligand



**Scheme 1** Structures of ligands and labeling for NMR spectroscopic assignment of **H<sub>2</sub>2**.



**Scheme 2** Catalytic asymmetric Henry reaction of 4-nitrobenzaldehyde and nitromethane.

1,6-bis(ethoxy-2-hydroxyphenyl)-(3*S*,4*S*)-(–)-diphenyl-2,5-diazaheptane (**H<sub>2</sub>2**, Scheme 2) as catalysts in the asymmetric Henry reaction, including an assessment of the scope of the most effective catalyst tested which uses **H<sub>2</sub>2** with two equivalents of CuI, and gives both excellent yield and enantioselectivity.

## Experimental

### General

Commercially available chemicals were of reagent grade and used without further purification. <sup>1</sup>H and <sup>13</sup>C NMR spectra

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were recorded on Bruker DRX-500 or DPX-400 MHz spectrometers; chemical shifts for  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are referenced to residual solvent peaks with respect to  $\text{TMS} = \delta$  0 ppm. Infrared spectra were recorded on a Shimadzu FTIR-8400S spectrophotometer with solid samples on a Golden Gate diamond ATR accessory. Solution 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, integrator on a Hewlett Packard S1100 instrument using Chiralcel OD-H or AD-H columns. Optical rotations were measured using a Perkin Elmer Polarimeter 341, sodium lamp, 1 dm cuvette lengths,  $c$  in g per 100 mL. The circular dichroism (CD) spectrum of ligand **H<sub>2</sub>2** was recorded on a DS62 spectropolarimeter (Aviv Associates, Lakewood, NJ) using Chirascan software (Applied Biophysics Ltd, Leatherhead, UK).

Ligand **H<sub>2</sub>1** was prepared as previously reported.<sup>34</sup> (1*S*,2*S*)-(–)-1,2-Diphenylethane-1,2-diamine (Fluka) and 3-ethoxysalicylaldehyde were used as received (Sigma-Aldrich).

## H<sub>2</sub>2

A solution of (1*S*,2*S*)-(–)-1,2-diphenylethane-1,2-diamine (0.42 g, 2.0 mmol) in MeOH (10 cm<sup>3</sup>) was added dropwise to a stirred solution of 3-ethoxysalicylaldehyde (0.67 g, 4.0 mmol) in MeOH (20 cm<sup>3</sup>). The resulting mixture was heated at reflux for 2 h. After cooling to room temperature, solid NaBH<sub>4</sub> (0.38 g, 10.0 mmol) was added in small portions over a period of 1 h. The resulting colourless solution was allowed to stir at room temperature overnight, after which, the solvent was removed *in vacuo*, and water (100 cm<sup>3</sup>) added, and extracted with CHCl<sub>3</sub> (3 × 50 cm<sup>3</sup>). The combined organic solutions were washed with water and brine, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solution was filtered and concentrated under reduced pressure to give a colourless oil, which was purified by column chromatography (SiO<sub>2</sub>, hexane–EtOAc 4 : 1 with 5% MeOH). **H<sub>2</sub>2** was isolated as a white solid (0.87 g, 85%). mp 78–80 °C.  $^1\text{H}$  NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 7.16 (overlapping, 6H, H<sup>B3+B4</sup>), 6.98 (d,  $J$  = 7.6 Hz, 4H, H<sup>B2</sup>), 6.75 (d,  $J$  = 8.0 Hz, 2H, H<sup>A4</sup>), 6.65 (t,  $J$  = 7.8 Hz, 2H, H<sup>A5</sup>), 6.48 (d,  $J$  = 7.5 Hz, 2H, H<sup>A6</sup>), 4.07 (q,  $J$  = 7.1 Hz, 4H, H<sup>CH<sub>2</sub>CH<sub>3</sub></sup>), 4.06 (q,  $J$  = 6.9 Hz, 4H, H<sup>CH<sub>2</sub>CH<sub>3</sub></sup>), 3.88 (s, 2H, H<sup>b</sup>), 3.79 (d,  $J$  = 13.4 Hz, 2H, H<sup>a1</sup>), 3.55 (d,  $J$  = 13.4 Hz, 2H, H<sup>a2</sup>), 1.44 (t,  $J$  = 7.0 Hz, 6H, H<sup>CH<sub>2</sub>CH<sub>3</sub></sup>);  $^{13}\text{C}$  NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 147.0 (C<sup>A3</sup>), 146.6 (C<sup>A2</sup>), 138.7 (C<sup>B1</sup>), 128.5 (C<sup>B2/B3</sup>), 128.3 (C<sup>B2/B3</sup>), 127.8 (C<sup>B4</sup>), 123.9 (C<sup>A1</sup>), 121.1 (C<sup>A6</sup>), 119.1 (C<sup>A5</sup>), 112.0 (C<sup>A4</sup>), 67.8 (C<sup>b</sup>), 64.5 (C<sup>CH<sub>2</sub>CH<sub>3</sub></sup>), 49.5 (C<sup>a</sup>), 15.2 (C<sup>CH<sub>2</sub>CH<sub>3</sub></sup>); IR (solid, cm<sup>−1</sup>) 3264w, 2974w, 2892w, 1585m, 1469s, 1393m, 1251s, 1230s, 1113m, 1068s, 1036s, 954m, 866m, 836m, 770s, 738s, 698s; UV/VIS  $\lambda_{\text{max}}$ /nm (2.19 × 10<sup>−5</sup> mol dm<sup>−3</sup>, THF) 240 ( $\epsilon$ /10<sup>3</sup> dm<sup>3</sup> mol<sup>−1</sup> cm<sup>−1</sup> 7.2), 264 sh (4.4), 290 (3.4); ESI-MS (MeOH)  $m/z$  513.4 [M + H]<sup>+</sup> (base peak, calc. 513.3), 535.3 [M + Na]<sup>+</sup> (calc. 535.3). Found C 73.04, H 7.12, N 4.92%; C<sub>32</sub>H<sub>36</sub>N<sub>2</sub>O<sub>4</sub>·0.7H<sub>2</sub>O requires C 73.17, H 7.18, N 5.33%. [ $\alpha$ ]<sub>D</sub><sup>20</sup> = −8.3 ( $c$  = 0.5, CH<sub>2</sub>Cl<sub>2</sub>). The CD spectrum of the ligand is shown in Fig. S1, ESI†.

## [Cu(2)]

A solution of Cu(OAc)<sub>2</sub> (18.1 mg, 0.100 mmol) in MeOH (5 cm<sup>3</sup>) was added to a solution of **H<sub>2</sub>2** (51.2 mg, 0.100 mmol) in MeOH (5 cm<sup>3</sup>) at room temperature. A pale green suspension formed upon stirring the reaction mixture for 30 min. The product was separated by filtration and was washed with MeOH (5 cm<sup>3</sup>). After drying *in vacuo*, [Cu(2)] was isolated as a green solid (47.0 mg, 82%). IR (solid, cm<sup>−1</sup>) 3200m, 2970w, 1589m, 1473s, 1452s, 1444s, 1321w, 1284m, 1231s, 1086m, 1036m, 1013m, 978m, 965m, 937w, 877w, 851s, 770m, 745s, 701s; ESI-MS (MeOH)  $m/z$  596.1 [M + Na]<sup>+</sup> (base peak, calc. 596.2). Found C 65.85, H 5.94, N 4.56%; C<sub>32</sub>H<sub>34</sub>CuN<sub>2</sub>O<sub>4</sub>·0.6MeOH requires C 65.98, H 6.18, N 4.72%.

## [<sup>1</sup>Pr<sub>2</sub>EtNH]<sub>m</sub>[Cu<sub>2</sub>I<sub>3</sub>]<sub>n</sub>

**H<sub>2</sub>2** (10.2 mg, 0.02 mmol) was dissolved in THF (0.8 cm<sup>3</sup>) in a screw-capped vial containing a stir bar at room temperature. CuI (0.04 mmol, 2.0 equiv.) was added in one portion, and the resulting brown suspension was stirred for 30 min. Diisopropylethylamine (2.0 equiv.) was added by syringe, and the mixture was stirred for another 10 min. After the addition of nitromethane (0.3 cm<sup>3</sup>), the resulting pale-green solution was filtered. The filtrate was transferred to a small vial and diethyl ether was allowed to diffuse slowly into the solution over a period of 3 days. X-Ray quality colourless crystals formed. ESI-MS (MeOH–H<sub>2</sub>O):  $m/z$  130.2 [<sup>1</sup>Pr<sub>2</sub>EtNH]<sup>+</sup> (calc. 130.2).

## 1.33[Cu(2)]·0.67H<sub>2</sub>2

**H<sub>2</sub>2** (5.1 mg, 0.01 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub>–EtOH (1.5 cm<sup>3</sup>, 1 : 2, v/v) in a screw-capped vial containing a stirring bar. CuCl (0.02 mmol, 2.0 equiv.) was added in one portion, and the brown suspension was stirred at room temperature for 30 min, after which it was filtered. Solvent from the filtrate was allowed to evaporate slowly at room temperature and after one week, yielded brown block-like crystals. ESI-MS (CH<sub>2</sub>Cl<sub>2</sub>–MeOH):  $m/z$  596.1 [M + Na]<sup>+</sup> (base peak, calc. 596.2), 513.4 [H<sub>2</sub>2 + H]<sup>+</sup> (calc. 513.3).

## Crystal structure determinations

Data were collected on Bruker-Nonius Kappa CCD or Stoe IPDS diffractometers; data reduction, solution and refinement used the programs COLLECT,<sup>45</sup> SIR92,<sup>46</sup> DENZO/SCALEPACK<sup>47</sup> and CRYSTALS,<sup>48</sup> or Stoe IPDS software<sup>49</sup> and SHELXL97.<sup>50</sup> Structures have been analyzed using Mercury v. 2.2.<sup>51</sup>

## [Cu(2)]

C<sub>32</sub>H<sub>34</sub>CuN<sub>2</sub>O<sub>4</sub>,  $m$  = 574.18, green needle, monoclinic, space group C<sub>2</sub>,  $a$  = 20.1947(8),  $b$  = 14.0122(8),  $c$  = 9.4085(5) Å,  $\beta$  = 96.926(4)°,  $U$  = 2642.9(2) Å<sup>3</sup>,  $z$  = 4,  $D_c$  = 1.443 Mg m<sup>−3</sup>,  $\mu$ (Mo–K $\alpha$ ) = 0.868 mm<sup>−1</sup>,  $T$  = 123 K. Total 76 654 reflections, 12 023 unique,  $R_{\text{int}}$  = 0.041. Refinement of 8030 reflections (354 parameters) with  $I > 2\sigma(I)$  converged at final  $R_1$  = 0.0266 ( $R_1$  all data = 0.0403),  $wR_2$  = 0.0281 ( $wR_2$  all data = 0.0359),  $\text{gof}$  = 1.069.

**[<sup>i</sup>Pr<sub>2</sub>EtNH][Cu<sub>2</sub>I<sub>3</sub>]<sub>n</sub>**

C<sub>8</sub>H<sub>20</sub>Cu<sub>2</sub>I<sub>3</sub>N, *m* = 638.06, colourless plate, monoclinic, space group *P*2<sub>1</sub>/*n*, *a* = 8.4552(2), *b* = 17.3368(4), *c* = 10.8328(2) Å, β = 95.462(1)°, *U* = 1580.73(6) Å<sup>3</sup>, *z* = 4, *D*<sub>c</sub> = 2.681 Mg m<sup>-3</sup>, μ(Mo-K<sub>α</sub>) = 8.521 mm<sup>-1</sup>, *T* = 123 K. Total 69 573 reflections, 7681 unique, *R*<sub>int</sub> = 0.032. Refinement of 5956 reflections (127 parameters) with *I* > 2σ(*I*) converged at final *R*<sub>1</sub> = 0.0178 (*R*<sub>1</sub> all data = 0.0271), *wR*<sub>2</sub> = 0.0167 (*wR*<sub>2</sub> all data = 0.0276), *gof* = 1.0936.

**1.33[Cu(2)]·0.67H<sub>2</sub>O**

C<sub>64</sub>H<sub>69.34</sub>Cu<sub>1.33</sub>N<sub>4</sub>O<sub>8</sub>, *m* = 1107.10, brown block, monoclinic, space group *C*<sub>2</sub>, *a* = 20.412(4), *b* = 13.926(3), *c* = 9.434(2) Å, β = 97.94(3)°, *U* = 2656.0(10) Å<sup>3</sup>, *z* = 2, *D*<sub>c</sub> = 1.385 Mg m<sup>-3</sup>, μ(Mo-K<sub>α</sub>) = 0.605 mm<sup>-1</sup>, *T* = 173(2) K. Total 53 792 reflections, 8697 unique, *R*<sub>int</sub> = 0.0371. Refinement of 8662 reflections (371 parameters) with *I* > 2σ(*I*) converged at final *R*<sub>1</sub> = 0.0396 (*R*<sub>1</sub> all data = 0.0397), *wR*<sub>2</sub> = 0.1288 (*wR*<sub>2</sub> all data = 0.1289), *gof* = 1.127.

**Typical procedure for asymmetric Henry reaction**

This procedure corresponds to entry 14 in Table 3. H<sub>2</sub>O (5.1 mg, 0.010 mmol, 0.050 equiv.) was dissolved in THF (0.4 cm<sup>3</sup>) contained in a screw-capped vial equipped with a stir bar at room temperature. CuI (3.8 mg, 0.020 mmol, 0.10 equiv.) was added in one portion and the resulting brown suspension was stirred for 30 min. Diisopropylethylamine (1.3 mg, 0.010 mmol, 0.050 equiv.) was then added by syringe, and the mixture stirred for a further 10 min. After cooling to 273 K, nitromethane (0.13 cm<sup>3</sup>, 1.0 mmol, 5.0 equiv.) and 4-nitrobenzaldehyde (30 mg, 0.2 mmol, 1.0 equiv.) were added sequentially. The mixture was then stirred at 273 K for 12 h after which the volatile components were removed under reduced pressure and the crude product purified by column chromatography (SiO<sub>2</sub>, hexane–EtOAc, 3 : 1 v/v) to give the nitroaldol product as a pale-yellow solid (42 mg, 99%). (*R*)-2-Nitro-1-(4-nitrophenyl)ethanol: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ/ppm 8.27 (d, *J* = 8.8 Hz, 2H, H<sup>Ar</sup>), 7.63 (d, 2H, *J* = 8.4 Hz, H<sup>Ar</sup>), 5.61 (m, 1H, H<sup>CHOH</sup>), 4.61 (dd, *J* = 14.0, 8.4 Hz, 1H, H<sup>CH<sub>2</sub></sup>), 4.56 (dd, *J* = 13.6, 4.0 Hz, 1H, H<sup>CH<sub>2</sub></sup>), 3.14 (d, *J* = 4.0 Hz, 1H, H<sup>OH</sup>). Enantiomeric excess (HPLC, 85 : 15, heptane–isopropanol, 0.8 mL min<sup>-1</sup>, 230 nm): major enantiomer *T*<sub>r</sub> = 18.8 min, minor enantiomer *T*<sub>r</sub> = 23.6 min; 92% ee; [α]<sub>D</sub><sup>20</sup> –31.2 (*c* = 0.6, CH<sub>2</sub>Cl<sub>2</sub>). The absolute configuration of the Henry product was assigned as *R* by comparison of the optical rotation with literature data.<sup>16</sup>

**(*R*)-2-Nitro-1-(2-nitrophenyl)ethanol**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ/ppm 8.08 (dd, *J* = 8.0, 1.2 Hz, 1H, H<sup>Ar</sup>), 7.96 (dd, *J* = 8.0, 1.2 Hz, 1H, H<sup>Ar</sup>), 7.75 (m, 1H, H<sup>Ar</sup>), 7.55 (m, 1H, H<sup>Ar</sup>), 6.05 (dt, *J* = 8.8, 2.4 Hz, 1H, H<sup>CHOH</sup>), 4.88 (dd, *J* = 13.6, 2.2 Hz, 1H, H<sup>CH<sub>2</sub></sup>), 4.56 (dd, *J* = 13.6, 9.2 Hz, 1H, H<sup>CH<sub>2</sub></sup>), 3.17 (d, *J* = 4.4 Hz, 1H, H<sup>OH</sup>). Enantiomeric excess (HPLC, 85 : 15 heptane–isopropanol, 0.8 mL min<sup>-1</sup>, 250 nm): major enantiomer *T*<sub>r</sub> = 12.3 min, minor enantiomer *T*<sub>r</sub> = 14.2 min; 95% ee; [α]<sub>D</sub><sup>20</sup> +206.6 (*c* = 0.5, CH<sub>2</sub>Cl<sub>2</sub>).<sup>27</sup>

**(*R*)-2-Nitro-1-(3-nitrophenyl)ethanol**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ/ppm 8.32 (s, 1H, H<sup>Ar</sup>), 8.23 (m, 1H, H<sup>Ar</sup>), 7.77 (d, *J* = 7.6 Hz, 1H, H<sup>Ar</sup>), 7.62 (t, *J* = 8.0 Hz, 1H, H<sup>Ar</sup>), 5.61 (m, 1H, H<sup>CHOH</sup>), 4.60 (d, *J* = 3.2 Hz, 1H, H<sup>CH<sub>2</sub></sup>), 4.50–4.70 (m, 1H, H<sup>OH</sup>), 3.15 (d, 1H, *J* = 4.0 Hz, H<sup>CH<sub>2</sub></sup>). Enantiomeric excess (HPLC, 85 : 15 heptane–isopropanol, 0.8 mL min<sup>-1</sup>, 250 nm): major enantiomer *T*<sub>r</sub> = 18.2 min, minor enantiomer *T*<sub>r</sub> = 20.9 min; 91% ee; [α]<sub>D</sub><sup>20</sup> –32.0 (*c* = 0.5, CH<sub>2</sub>Cl<sub>2</sub>).<sup>35</sup>

**(*R*)-1-(4-cyanophenyl)-2-nitroethanol**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ/ppm 7.71 (d, *J* = 8.0 Hz, 2H, H<sup>Ar</sup>), 7.56 (d, *J* = 8.0 Hz, 2H, H<sup>Ar</sup>), 5.55 (m, 1H, H<sup>CHOH</sup>), 4.56 (m, 2H, H<sup>CH<sub>2</sub></sup>), 3.08 (br, 1H, H<sup>OH</sup>). Enantiomeric excess (HPLC, 80 : 20 heptane–isopropanol, 0.8 mL min<sup>-1</sup>, 250 nm): major enantiomer *T*<sub>r</sub> = 13.5 min, minor enantiomer *T*<sub>r</sub> = 15.6 min; 90% ee; [α]<sub>D</sub><sup>20</sup> –32.8 (*c* = 0.50, CH<sub>2</sub>Cl<sub>2</sub>).<sup>52</sup>

**(*R*)-2-Nitro-1-(pyridin-3-yl)ethanol**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ/ppm 8.62 (s, 1H, H<sup>Py</sup>), 8.57 (d, *J* = 5.2 Hz, 1H, H<sup>Py</sup>), 7.80 (m, 1H, H<sup>Py</sup>), 7.36 (dd, *J* = 7.6, 4.8 Hz, 1H, H<sup>Py</sup>), 5.54 (dd, *J* = 9.6, 3.2 Hz, 1H, H<sup>CHOH</sup>), 4.64 (dd, *J* = 13.2, 9.6 Hz, 1H, H<sup>CH<sub>2</sub></sup>), 4.56 (dd, *J* = 13.2, 3.6 Hz, 1H, H<sup>CH<sub>2</sub></sup>), 4.7 (br, 1H, H<sup>OH</sup>). Enantiomeric excess: (HPLC, 75 : 25 heptane–isopropanol, 0.7 mL min<sup>-1</sup>, 250 nm); major enantiomer *T*<sub>r</sub> = 15.2 min, minor enantiomer *T*<sub>r</sub> = 28.7 min; 91% ee; [α]<sub>D</sub><sup>20</sup> –38.6 (*c* = 0.6, CH<sub>2</sub>Cl<sub>2</sub>).<sup>53</sup>

**(*R*)-2-Nitro-1-(pyridin-4-yl)ethanol**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ/ppm 8.62 (dd, *J* = 4.8, 1.6 Hz, 2H, H<sup>Py</sup>), 7.37 (m, 2H, H<sup>Py</sup>), 5.50 (dd, *J* = 7.6, 4.8 Hz, 1H, H<sup>CHOH</sup>), 4.58 (m, 2H, H<sup>CH<sub>2</sub></sup>), 3.70 (br, 1H, H<sup>OH</sup>). Enantiomeric excess: (HPLC, 75 : 25 heptane–isopropanol, 0.7 mL min<sup>-1</sup>, 220 nm); major enantiomer *T*<sub>r</sub> = 11.8 min, minor enantiomer *T*<sub>r</sub> = 14.4 min; 92% ee; [α]<sub>D</sub><sup>20</sup> –31.2 (*c* = 0.7, CH<sub>2</sub>Cl<sub>2</sub>).<sup>54</sup>

**(2*R*,3*E*)-1-Nitro-4-phenylbut-3-en-2-ol**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ/ppm 7.38 (m, 5H, H<sup>Ar</sup>), 6.80 (d, *J* = 16.0 Hz, 1H, H<sup>ArCH=CH</sup>), 6.15 (dd, *J* = 16.0, 8.0 Hz, 1H, H<sup>ArCH=CH</sup>), 5.06 (m, 1H, H<sup>CHOH</sup>), 4.53 (m, 1H, H<sup>CH<sub>2</sub></sup>), 2.60 (br, 1H, H<sup>OH</sup>). Enantiomeric excess: (HPLC, 80 : 20 heptane–isopropanol, 0.6 mL min<sup>-1</sup>, 250 nm); minor enantiomer *T*<sub>r</sub> = 28.0 min, major enantiomer *T*<sub>r</sub> = 31.8 min; 95% ee; [α]<sub>D</sub><sup>20</sup> –7.4 (*c* = 0.25, CH<sub>2</sub>Cl<sub>2</sub>).<sup>27</sup>

**(*R*)-1-Nitro-3-phenylpropan-2-ol**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ/ppm 7.34 (m, 5H, H<sup>Ar</sup>), 4.56 (m, 1H, H<sup>CHOH</sup>), 4.42 (m, 2H, H<sup>CH<sub>2</sub>NO<sub>2</sub></sup>), 3.05 (m, 1H, H<sup>OH</sup>), 2.87 (dd, *J* = 16.0, 8.0 Hz, 2H, H<sup>ArCH<sub>2</sub></sup>). Enantiomeric excess: (HPLC, 90 : 10 heptane–isopropanol, 0.8 mL min<sup>-1</sup>, 210 nm); major enantiomer *T*<sub>r</sub> = 20.6 min, minor enantiomer *T*<sub>r</sub> = 26.2 min; 90% ee; [α]<sub>D</sub><sup>20</sup> +5.2 (*c* = 0.20, CH<sub>2</sub>Cl<sub>2</sub>).<sup>55</sup>

**(*R*)-1-Cyclohexyl-2-nitroethanol**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ/ppm 4.48 (dd, *J* = 13.2, 3.2 Hz, 1H, H<sup>CH<sub>2</sub>NO<sub>2</sub></sup>), 4.41 (dd, *J* = 13.2, 8.8 Hz, 1H, H<sup>CH<sub>2</sub>NO<sub>2</sub></sup>), 4.10 (m, 1H, H<sup>CHOH</sup>), 2.44 (d, *J* = 5.2 Hz, 1H, H<sup>OH</sup>), 1.80 (m, 3H, H<sup>Cy</sup>), 1.68 (m, 2H, H<sup>Cy</sup>), 1.46 (m, 1H, H<sup>Cy</sup>), 1.19

(m, 5H,  $H^{Cy}$ ). Enantiomeric excess: (HPLC, 97 : 3 heptane–isopropanol, 0.8 mL min<sup>-1</sup>, 210 nm); major enantiomer  $T_r$  = 28.6 min, minor enantiomer  $T_r$  = 30.8 min; 88% ee;  $[\alpha]_D^{20}$  -15.8 ( $c$  = 1.0, CH<sub>2</sub>Cl<sub>2</sub>).<sup>16</sup>

### (*R*)-1-Nitrohexan-2-ol

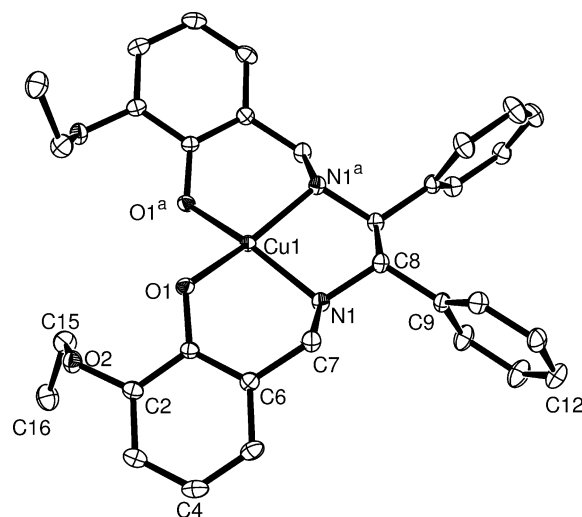
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm 4.43 (dd,  $J$  = 12.8, 2.8 Hz, 1H,  $H^{CH_2NO_2}$ ), 4.37 (dd, 1H,  $J$  = 12.4, 8.4 Hz,  $H^{CH_2NO_2}$ ), 4.32 (m, 1H,  $H^{CHOH}$ ), 2.52 (d,  $J$  = 4.8 Hz, 1H,  $H^{OH}$ ), 1.43 (m, 6H,  $H^{CH_2}$ ), 0.92 (t,  $J$  = 6.4 Hz, 3H,  $H^{CH_3}$ ). Enantiomeric excess: (HPLC, 98 : 2 heptane–isopropanol, 0.6 mL min<sup>-1</sup>, 210 nm); major enantiomer  $T_r$  = 39.0 min, minor enantiomer  $T_r$  = 50.5 min; 94% ee;  $[\alpha]_D^{20}$  -9.2 ( $c$  = 0.6, CH<sub>2</sub>Cl<sub>2</sub>).<sup>16</sup>

## Results and discussion

### Syntheses and characterization of H<sub>2</sub>2 and [Cu(2)]

The reduced Schiff base H<sub>2</sub>2 was prepared by routine methodology involving the condensation of 3-ethoxysalicylaldehyde with (1*S*,2*S*)-(–)-1,2-diphenylethane-1,2-diamine followed by reduction of the intermediate bis(imine) by NaBH<sub>4</sub>. The electrospray mass spectrum of the compound exhibited a base peak at  $m/z$  513.4 assigned to  $[M + H]^+$  and a higher mass peak at  $m/z$  535.3 arising from  $[M + Na]^+$ . The <sup>1</sup>H and <sup>13</sup>C NMR spectra were assigned by 2D techniques and were in complete accord with the structure shown in Scheme 1. The signal for proton  $H^{A4}$  was assigned from a NOESY cross peak to the resonance for the ethyl CH<sub>2</sub> group, and that for  $H^{B2}$  from the NOESY cross peak to the signal for  $H^b$ . The diastereotopic protons  $H^a$  appear as two doublets ( $J$  = 13.4 Hz) at  $\delta$  3.55 and 3.79 ppm. The signal assigned to the ethyl CH<sub>3</sub> groups appears as a clean triplet ( $\delta$  1.44 ppm), but the resonances for the ethyl CH<sub>2</sub> groups appear as two overlapping quartets ( $\delta$  4.07 and 4.06 ppm), indicating that these methylene groups sense the presence of the stereogenic centers. The CD spectrum of H<sub>2</sub>2 is shown in Fig. S1, ESI†.

The reaction of H<sub>2</sub>2 with copper(II) acetate in methanol resulted in the formation of pale green [Cu(2)]. The base peak in the electrospray mass spectrum ( $m/z$  596.1) corresponded to  $[M + Na]^+$  and exhibited the corrected isotopologue distribution for this ion. X-Ray quality crystals of [Cu(2)] were obtained by slow diffusion of Et<sub>2</sub>O into an EtOH–CHCl<sub>3</sub> solution of the complex over a period of two weeks. The complex crystallizes in the chiral space group *C*<sub>2</sub>. The asymmetric unit contains two crystallographically independent, but structurally similar, half-molecules (labelled A and B). The structure of molecule A is shown in Fig. 1, and selected bond parameters for both molecules are given in the figure caption. In molecule A, atom Cu1 resides on the special position 0,  $y$ , 1/2, while in molecule B, atom Cu2 is sited on the special position 0,  $y$ , 0. Since these correspond to the Cu atoms being on 2-fold axes, the ethyl groups necessarily point up and down on either side of the coordination plane. Molecules of [Cu(2)] stack in columns that run parallel to the *c*-axis and as a consequence of the crystal symmetry, all Cu...Cu non-bonded separations along the stack are equal (4.7429(3) Å). The molecular structure differs from that of [Cu(1)]<sup>34,56</sup> in two respects. Firstly, the *O,O',O'',O'''*-cavity in



**Fig. 1** Molecular structure of one of the two independent molecules (molecule A) of [Cu(2)] with ellipsoids plotted at the 50% probability level, and H atoms omitted. Selected bond parameters for molecule A: Cu1–N1 = 2.023(2), Cu1–O1 = 1.917(1) Å; N1–Cu1–O1 = 94.24(5)°, N1–Cu1–N1<sup>a</sup> = 84.01(8)°, O1–Cu1–O1<sup>a</sup> = 93.57(6)°, N1–Cu1–O1<sup>a</sup> = 160.69(5)°. For molecule B: Cu2–N2 = 2.024(1), Cu2–O3 = 1.923(1) Å; N2–Cu2–O3 = 93.55(5)°, N2–Cu2–N2<sup>b</sup> = 85.23(8)°, O3–Cu2–O3<sup>b</sup> = 89.80(6)°, O3<sup>b</sup>–Cu2–N2 = 168.69(5)°. Symmetry codes: *a* = 1 – *x*, *y*, 1 – *z*; *b* = 1 – *x*, *y*, –*z*.

[Cu(1)] acts as a host for a water molecule. Secondly, there is face-to-face stacking of pairs of [Cu(1)] molecules with a non-bonded Cu...Cu separation of 3.816(1) Å; although the overall packing involves stacking of pairs, the second Cu...Cu separation is significantly longer than the first (5.642(1) Å).

### Catalyst screening: copper(II) salts

In our previous studies<sup>34</sup> of the asymmetric Henry reaction, we tested the catalytic activity of three pre-prepared chiral copper(II) complexes. We concluded that [Cu(1)], which contains a reduced Schiff base ligand, gave better yields and enantioselectivities in the reaction shown in Scheme 2 than two complexes which contained the related imine ligands. The catalysts were tested in the absence and presence of added metal salts, and we noted that the activity was enhanced when a second equivalent of Cu(OAc)<sub>2</sub> was added to the catalyst [Cu(1)].

The catalytic tests described below were designed to address a number of points, and all focused on the asymmetric Henry reaction depicted in Scheme 2. The enantiomeric excess of the product was determined by HPLC. All the reactions detailed in Tables 1 and 2 were carried out on a 0.20 mmol scale with 5 mol% of H<sub>2</sub>2 and 5 mol% of metal salt at a 0.5 mol dm<sup>-3</sup> concentration, and using 5.0 equivalents of nitromethane in the solvents stated in the tables. The absolute configuration of the  $\beta$ -hydroxynitroalkane was assigned as (*R*) by comparison with the optical rotation in the literature (see Experimental section). We initially looked at the effects of ligand modification, starting with a comparison of the performances of H<sub>2</sub>1 and H<sub>2</sub>2 in the presence of Cu(OAc)<sub>2</sub> in ethanol (Table 1, entries 1 and 2). Both yield and enantioselectivity are enhanced with the new reduced Schiff base H<sub>2</sub>2. Entry 3 in



**Table 1** Results for initial screening using ligand **H<sub>2</sub>2** in the catalytic asymmetric Henry reaction shown in Scheme 2

Entry	Ligand	Metal salt	Solvent	T/K	Time/h	Yield <sup>a</sup> (%)	ee <sup>b</sup> (%)
1	<b>H<sub>2</sub>1</b>	Cu(OAc) <sub>2</sub>	EtOH	295	60	86	23
2	<b>H<sub>2</sub>2</b>	Cu(OAc) <sub>2</sub>	EtOH	295	18	98	70
3	<b>H<sub>2</sub>2</b>	None	EtOH	295	18	42	0
4	<b>H<sub>2</sub>2</b>	Cu(OTf) <sub>2</sub>	EtOH	295	18	<5	n.d. <sup>c</sup>
5	<b>H<sub>2</sub>2</b>	CuCl <sub>2</sub>	EtOH	295	18	<5	n.d.
6	<b>H<sub>2</sub>2</b>	CuSO <sub>4</sub>	EtOH	295	48	40	6
7	<b>H<sub>2</sub>2</b>	Cu(OAc) <sub>2</sub>	MeOH	295	18	65	55
8	<b>H<sub>2</sub>2</b>	Cu(OAc) <sub>2</sub>	Toluene	295	18	40	71
9	<b>H<sub>2</sub>2</b>	Cu(OAc) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	295	18	47	60
10	<b>H<sub>2</sub>2</b>	Cu(OAc) <sub>2</sub>	THF	295	18	95	86
11	<b>H<sub>2</sub>2</b>	Cu(OAc) <sub>2</sub>	THF	273	18	92	85

<sup>a</sup> Isolated yield after chromatographic purification. <sup>b</sup> Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column.

<sup>c</sup> n.d. = not determined.

**Table 2** Results of catalytic screening using ligand **H<sub>2</sub>2** and Cu(OAc)<sub>2</sub> in the presence of a second metal ion in the asymmetric Henry reaction shown in Scheme 2<sup>a</sup>

Entry	Second metal salt added	Time/h	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	Cu(OAc) <sub>2</sub>	18	94	84
2	Cu(OTf) <sub>2</sub>	48	<5	n.d. <sup>d</sup>
3	CuCl	65	72	82
4	Pd(OAc) <sub>2</sub>	24	86	68
5	Ni(OAc) <sub>2</sub>	16	90	21
6	Co(OAc) <sub>2</sub>	16	91	0
7	KBr	24	48	6
8	NaI	16	65	2

<sup>a</sup> All reactions were carried out on a 0.20 mmol scale with 5 mol% of **H<sub>2</sub>2** and of Cu(OAc)<sub>2</sub>, and 5 mol% of the second metal salt at a 0.5 M concentration using 5.0 equivalents of nitromethane in THF at 295 K.

<sup>b</sup> Isolated yield after chromatographic purification. <sup>c</sup> Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column.

<sup>d</sup> n.d. = not determined.

Table 1 confirms that, in the absence of Cu(OAc)<sub>2</sub>, the reaction is not enantioselective.

Retaining a common solvent (ethanol), metal ion (Cu<sup>2+</sup>) and ligand (**H<sub>2</sub>2**), we next looked at the effects of varying the anion. The results summarized in entries 2 and 4–6 in Table 1

confirm that the acetate salt gives the highest yield and enantioselectivity of those salts screened. A comparison of screening experiments 2 and 7–10 (Table 1) illustrates the effects of solvent on catalyst performance. Use of either ethanol or THF results in excellent yields of the β-hydroxynitro derivative. At 295 K, the enantioselectivity is optimized in THF (86% ee), and this is little affected when the reaction is carried out at 273 K over the same 18 hour period.

Previously, we have shown that both yield and enantioselectivity of the asymmetric Henry reaction in Scheme 2 are enhanced when a second equivalent of Cu(OAc)<sub>2</sub> is added to the [Cu(I)] catalyst.<sup>34</sup> Having established that yield and enantioselectivity in the chosen test reaction were optimized when using **H<sub>2</sub>2**, Cu(OAc)<sub>2</sub> in THF at 295 K, we screened a series of catalytic runs in the presence of different metal salts (Table 2). In each run, **H<sub>2</sub>2** was dissolved in THF and one equivalent of Cu(OAc)<sub>2</sub> was added. After ~10 minutes, one equivalent of the second metal salt was added, and the mixture was stirred at 295 K for ~30 minutes. The reagents for the asymmetric Henry reaction in Scheme 2 were then added and the reaction continued as described in the experimental section. A comparison of the data in Table 2 with entry 10 in Table 1 reveals that the addition of the second 5 mol% of Cu(OAc)<sub>2</sub> has only a small influence on the yield and enantioselectivity. No enhancement of catalytic activity was observed upon the addition of the other metal salts screened.

#### Catalyst screening: copper(i) salts

While the vast majority of copper-based catalysts for the asymmetric Henry reaction involve copper(II),<sup>10,14–28,30–32,34,37</sup> copper(i)-containing systems have also proved active.<sup>29,33,35,36</sup> An initial test using CuCl with **H<sub>2</sub>2** (1 : 1, 5 mol%) in ethanol (entry 1, Table 3) showed promising enantioselectivity for the reaction in Scheme 2, and this was enhanced (albeit at the expense of yield) by running the reaction in THF (entry 2, Table 3). Significantly better results were obtained when the loading of CuCl was increased to 10 mol%, the ligand **H<sub>2</sub>2** being present at a concentration of 5 mol%. Under these conditions, an 88% yield of the β-hydroxynitro derivative was obtained with 91% ee. We repeated the reactions using CuBr

**Table 3** Results of catalytic screening using ligand **H<sub>2</sub>2** with copper(i) salts in the asymmetric Henry reaction shown in Scheme 2<sup>a</sup>

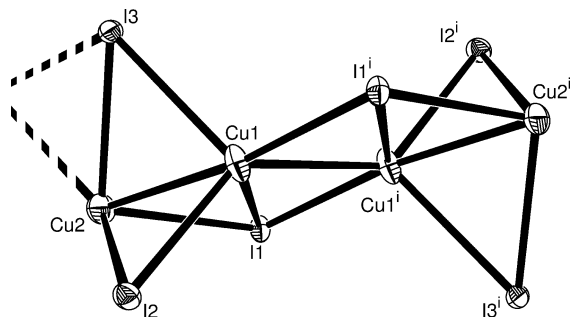
Entry	Metal salt	Loading of metal/mol%	Solvent	T/K	Time/h	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	CuCl	5	EtOH	295	48	61	81
2	CuCl	5	THF	295	65	34	90
3	CuCl	10	THF	295	65	88	91
4	CuBr	5	THF	295	65	32	72
5	CuBr	10	THF	295	65	<5	n.d. <sup>d</sup>
6	CuI	5	THF	295	65	64	93
7	CuI	10	THF	295	72	88	94
8	CuI	10	Toluene	295	65	27	15
9	CuI	10	CH <sub>2</sub> Cl <sub>2</sub>	295	65	36	9
10	CuI	10	1,4-Dioxane	295	65	54	74
11	CuI	10	MeCN	295	65	<5	n.d.
12 <sup>e</sup>	CuI	10	THF	295	2	99	87
13 <sup>f</sup>	CuI	10	THF	295	2	98	90
14 <sup>f</sup>	CuI	10	THF	273	12	99	92

<sup>a</sup> All reactions were performed on a 0.20 mmol scale with 5 mol% of ligand at a 0.5 M concentration using 5.0 equivalents of CH<sub>3</sub>NO<sub>2</sub> in the solvent indicated. <sup>b</sup> Isolated yields after chromatographic purification. <sup>c</sup> Enantiomeric excess determined by HPLC using a Chiralcel OD-H column. <sup>d</sup> n.d. = not determined. <sup>e</sup> 10 mol% <sup>i</sup>Pr<sub>2</sub>EtN was added. <sup>f</sup> 5 mol% <sup>i</sup>Pr<sub>2</sub>EtN was added.

or CuI in place of CuCl, with  $H_22$  : CuX ratios of 1 : 1 and 1 : 2. Entries 4–7 in Table 3 show that while the bromide gave poor results, a catalyst system involving 5 mol%  $H_22$  and 10 mol% CuI was highly effective. The use of THF as solvent appears to be preferable to the other solvents tested (entries 7–11, Table 3). Final tuning of the reaction conditions involved the addition of Hünig's base (diisopropylethylamine) and lowering of both the reaction time and temperature (entries 12–14, Table 3).

It is, of course, not necessarily the case that the active catalyst in the systems listed in Table 3 contains copper(I). Aerial oxidation to copper(II) is obviously possible with the Schiff base ligand stabilizing this oxidation state. We therefore attempted to crystallize species present in two of the copper(I)-based catalyst systems. In the first,  $H_22$  and CuI were combined in THF and the solution stirred in the presence of  $iPr_2EtNH$ , followed by addition of nitromethane. X-Ray quality colourless needles formed when  $Et_2O$  was allowed to diffuse slowly into the filtered reaction mixture. An electro-spray mass spectrum of this product (MeOH– $H_2O$ ) showed only a peak at  $m/z$  130.2 assigned to  $[iPr_2EtNH]^+$ . Structural analysis revealed the compound to be the copper(I) salt  $[iPr_2EtNH]_n[Cu_2I_3]_n$  containing polymeric anions (Fig. 2). The structure of the polymer is similar to those found in  $[K(12\text{-crown-}4)_2]_{2n}[Cu_4I_6]_n$ ,<sup>57</sup>  $[K(15\text{-crown-}5)]_{2n}[Cu_4I_6]_n$ ,<sup>58</sup>  $[Na(15\text{-crown-}5)]_{2n}[Na(15\text{-crown-}5)(OH_2)]_{2n}[Cu_2I_4]_n[Cu_4I_6]_n$ ,<sup>59</sup>  $[Rb(12\text{-crown-}4)_2]_{2n}[Cu_2I_3]_n$ ,<sup>60</sup>  $[2,4,6\text{-Ph}_3C_5H_2S][Cu_2I_3]$ <sup>61</sup> and  $[Et_4N]_n[Cu_2I_3]_n$ .<sup>62</sup> The chains are propagated parallel to the crystallographic  $a$ -axis and are involved in hydrogen bonds to the  $[iPr_2EtNH]^+$  ions ( $N9H91\cdots I2 = 2.80$ ,  $N9\cdots I2 = 3.675(1)$  Å,  $N9-H91\cdots I2 = 166^\circ$ ;  $C3H31\cdots I2^{ii} = 3.09$ ,  $C3\cdots I2^{ii} = 3.898(2)$  Å,  $C3-H31\cdots I2^{ii} = 142^\circ$ ; symmetry code  $ii = ii = 2 - x, 1 - y, 1 - z$ ). The lack of the chiral ligand  $H_22$  in the crystallized product clearly indicates that the latter is not the catalytically active species. Nonetheless, the data suggest that copper(I) may survive the conditions used for the asymmetric Henry reaction (entries 12–14, Table 3).

In the second crystallization experiment, solid CuCl was added to a  $CH_2Cl_2$ – $EtOH$  solution of  $H_22$ . After being stirred for 30 minutes, the mixture was filtered, and slow evaporation of the solvent yielded brown block-like crystals. Whereas the

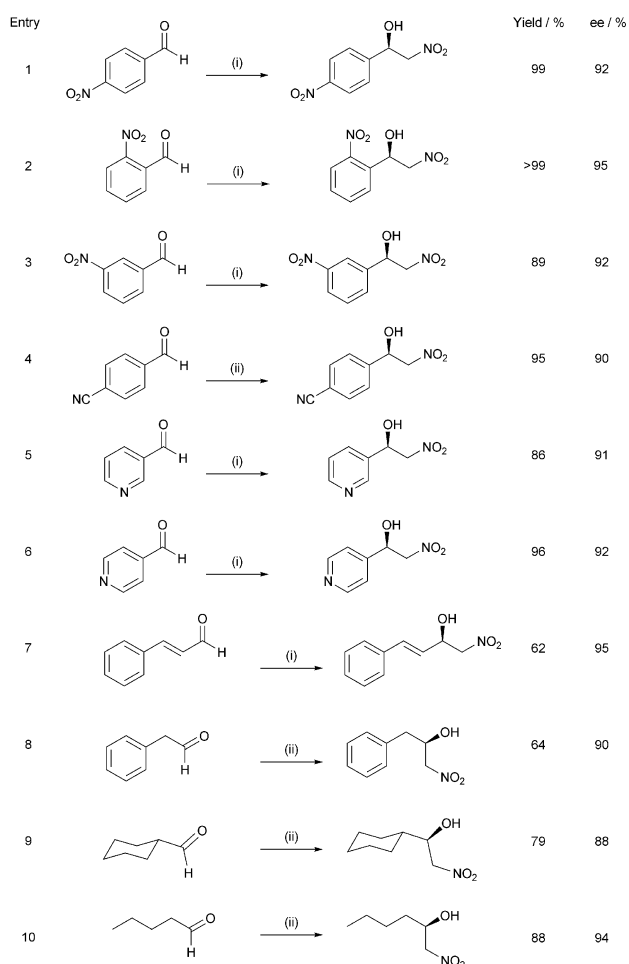


**Fig. 2** Part of one polymeric chain in  $[iPr_2EtNH]_n[Cu_2I_3]_n$  with ellipsoids plotted at the 50% probability level. Symmetry codes:  $i = 1 - x, 1 - y, 1 - z$ ;  $ii = 2 - x, 1 - y, 1 - z$ . Selected bond distances:  $I1-Cu1^i = 2.5382(3)$ ,  $I1-Cu1 = 2.7280(3)$ ,  $I1-Cu2 = 2.7903(3)$ ,  $I2-Cu1 = 2.6736(3)$ ,  $I2-Cu2 = 2.6764(3)$ ,  $I3-Cu2^{ii} = 2.5422(3)$ ,  $I3-Cu1 = 2.7841(3)$ ,  $I3-Cu2 = 2.7328(3)$ ,  $Cu1-Cu1^i = 2.6276(5)$ ,  $Cu1-Cu2 = 2.4900(3)$ ,  $Cu2-Cu2^{ii} = 2.6378(5)$  Å.

ESI mass spectrum of  $[Cu(2)]$  exhibits a base peak at  $m/z$  596.1 corresponding to  $[M + Na]^+$  and no other peaks with  $m/z > 443$ , the mass spectrum of the crystals showed a base peak at 596.1, and a peak with about one-third its intensity at  $m/z$  513.4 arising from  $[H_22 + H]^+$ . A single crystal structure determination confirmed the presence of  $1.33[Cu(2)] \cdot 0.67H_22$ , that is, cocrystallization of  $[Cu(2)]$  and  $H_22$ , with one-third of the ligand sites being substituted by another  $[Cu(2)]$  molecule. The gross structure is essentially the same as that of  $[Cu(2)]$  described earlier, but it is noteworthy that there is no change in conformation of the ligand upon binding of the  $Cu^{2+}$  ion in the  $N,N',O,O'$ -cavity of  $[2]^{2-}$ . In this case, oxidation of copper(I) to copper(II) occurs within a short time of mixing the components of the catalyst system (entry 3, Table 3).

### Extending the scope of the catalyst system

Once we had optimized the conditions (entries 13 and 14 in Table 3) for the enantioselective formation of (*R*)-2-nitro-1-(4-nitrophenyl)ethanol, we investigated the range of asymmetric Henry reactions to which these same conditions could be applied. All reactions were carried out on a 0.20 mmol scale. Fig. 3 illustrates that the conversion of aryl aldehydes with



**Fig. 3** Results of the enantioselective Henry reaction of nitromethane and selected aldehydes under optimized reaction conditions. (i)  $H_22$  (5 mol%), CuI (10 mol%), THF, 273 K, 12 h. (ii)  $H_22$  (5 mol%), CuI (10 mol%), THF, 295 K, 72 h.

electron-withdrawing substituents proceeds in high yield and with excellent enantioselectivity (entries 1–4 in Fig. 3). The pyridine derivatives were chosen as being representative of simple *N*-heterocyclic compounds, and both undergo transformation to the respective  $\beta$ -hydroxynitro derivative in high yield and with high enantioselectivity (entries 5 and 6, Fig. 3). The  $\beta$ -hydroxynitro derivatives of representative aliphatic aldehydes were obtained in moderate to good yields, and with excellent, or still acceptable, enantioselectivities. The reaction conditions proved not to be applicable to simple aromatic aldehydes (e.g. benzaldehyde) or aromatic aldehydes with electron-donating substituents (e.g. Cl, OMe, Me).

## Conclusions

We have tuned the components of a catalytic system for the asymmetric Henry reaction involving the reduced Schiff base ligand **H<sub>2</sub>2** and copper salts. Reaction conditions for the conversion of 4-nitrobenzaldehyde to 2-nitro-1-(4-nitrophenyl)-ethanol have been optimized (catalyst 5 mol% **H<sub>2</sub>2**, 10 mol% CuI, THF, 295 K and 2 hours or 273 K and 12 hours) resulting in 99% yield and 90–92% ee. These catalytic conditions are effective for other aromatic aldehydes containing electron-withdrawing substituents, and for pyridyl aldehydes; representative aliphatic aldehydes were converted to the respective  $\beta$ -hydroxynitro derivatives with good enantioselectivities, and in moderate yields. These catalytic conditions were found not to be effective for simple aromatic aldehydes or those containing electron-releasing substituents.

## Acknowledgements

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## Notes and references

- 1 L. Henry, *C. R. Hebd. Seances Acad. Sci.*, 1895, **120**, 1265.
- 2 G. Rosini, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, I. Fleming and C. H. Heathcock, Pergamon, New York, 1991, vol. 2, p. 321.
- 3 N. Ono, *The Nitro Group in Organic Synthesis*, Wiley-VCH, New York, 2001.
- 4 R. Ballini, A. Palmieria and P. Righi, *Tetrahedron*, 2007, **63**, 12099.
- 5 G. Rosini and R. Ballini, *Synthesis*, 1988, 833.
- 6 F. A. Luzzio, *Tetrahedron*, 2001, **57**, 915.
- 7 H. Sasai, T. Suzuki, S. Arai, T. Arai and M. Shibasaki, *J. Am. Chem. Soc.*, 1992, **114**, 4418.
- 8 C. Palomo, M. Oiarbide and A. Laso, *Eur. J. Org. Chem.*, 2007, 2561.
- 9 J. Boruwa, N. Gogoi, P. P. Saikia and N. C. Barua, *Tetrahedron: Asymmetry*, 2006, **17**, 3315.
- 10 C. Christensen, K. Juhl and K. A. Jørgensen, *Chem. Commun.*, 2001, 2222.
- 11 Y. Sohtome, Y. Kato, S. Handa, N. Aoyama, K. Nagawa, S. Matsunaga and M. Shibasaki, *Org. Lett.*, 2008, **10**, 2231.
- 12 B. Tan, P. J. Chua, X. Zeng, M. Lu and G. Zhong, *Org. Lett.*, 2008, **10**, 3489.
- 13 M. Bandini, R. Sinisi and A. Umani-Ronchi, *Chem. Commun.*, 2008, 4360.
- 14 T. Risgaard, K. V. Gothelf and K. A. Jørgensen, *Org. Biomol. Chem.*, 2003, **1**, 153.
- 15 C. Christensen, K. Juhl, R. G. Hazell and K. A. Jørgensen, *J. Org. Chem.*, 2002, **67**, 4875.
- 16 D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw and C. W. Downey, *J. Am. Chem. Soc.*, 2003, **125**, 12692.
- 17 M. Sedláček, P. Drabina, R. Keder, J. Hanusek, I. Cisařová and A. Růžicka, *J. Organomet. Chem.*, 2006, **691**, 2623.
- 18 C. Gan, G. Lai, Z. Zhang, Z. Wang and M.-M. Zhou, *Tetrahedron: Asymmetry*, 2006, **17**, 725.
- 19 S. K. Ginotra and V. K. Singh, *Org. Biomol. Chem.*, 2007, **5**, 3932.
- 20 K. Tanaka and S. Hachiken, *Tetrahedron Lett.*, 2008, **49**, 2533.
- 21 C. Gan, *Can. J. Chem.*, 2008, **86**, 261.
- 22 G. Blay, E. Climent, I. Fernández, V. Hernández-Olmos and J. R. Pedro, *Tetrahedron: Asymmetry*, 2007, **18**, 1603.
- 23 G. Blay, E. Climent, I. Fernández, V. Hernández-Olmos and J. R. Pedro, *Tetrahedron: Asymmetry*, 2006, **17**, 2046.
- 24 G. Blay, L. R. Domingo, V. Hernández-Olmos and J. R. Pedro, *Chem.-Eur. J.*, 2008, **14**, 4725.
- 25 G. Blay, V. Hernández-Olmos and J. R. Pedro, *Org. Biomol. Chem.*, 2008, **6**, 468.
- 26 G. Blay, V. Hernández-Olmos and J. R. Pedro, *Chem. Commun.*, 2008, 4840.
- 27 M. Bandini, F. Piccinelli, S. Tommasi, A. Umani-Ronchi and C. Ventrici, *Chem. Commun.*, 2007, 616.
- 28 M. Bandini, S. Cabiddu, E. Cadoni, P. Olivelli, R. Sinisi, A. Umani-Ronchi and M. Usai, *Chirality*, 2009, **21**, 239.
- 29 J.-J. Jiang and M. Shi, *Tetrahedron: Asymmetry*, 2007, **18**, 1376.
- 30 B. Qin, X. Xiao, X. Liu, J. Huang, Y. Wen and X. Feng, *J. Org. Chem.*, 2007, **72**, 9323.
- 31 M. Çolak and N. Demirel, *Tetrahedron: Asymmetry*, 2008, **19**, 635.
- 32 G. Lai, S. Wang and Z. Wang, *Tetrahedron: Asymmetry*, 2008, **19**, 1813.
- 33 C. Tan, X. Liu, L. Wang, J. Wang and X. Feng, *Org. Lett.*, 2008, **10**, 5305.
- 34 E. C. Constable, G. Zhang, C. E. Housecroft, M. Neuburger, S. Schaffner and W.-D. Woggon, *New J. Chem.*, 2009, **33**, 1064.
- 35 Y. Xiong, F. Wang, X. Wang, Y. Wen and X. Feng, *Chem.-Eur. J.*, 2007, **13**, 829.
- 36 B. Qin, X. Xiao, X. Liu, J. Huang, Y. Wen and X. Feng, *J. Org. Chem.*, 2007, **72**, 9323.
- 37 G. Zhang, E. Yashima and W.-D. Woggon, *Adv. Synth. Catal.*, 2009, **351**, 1255.
- 38 Y. Kogami, T. Nakajima, T. Ikeno and T. Yamada, *Synthesis*, 2004, 1947.
- 39 J. Park, K. Lang, K. A. Abboud and S. Hong, *J. Am. Chem. Soc.*, 2008, **130**, 16484.
- 40 R. Kowalczyk, Ł. Sidorowicz and J. Skarzewski, *Tetrahedron: Asymmetry*, 2007, **18**, 2581.
- 41 R. Kowalczyk, P. Kwiatkowski, J. Skarzewski and J. Jurczak, *J. Org. Chem.*, 2009, **74**, 753.
- 42 A. Zulauf, M. Mellah and E. Schulz, *J. Org. Chem.*, 2009, **74**, 2242.
- 43 Q. T. Nguyen and J. H. Jeong, *Bull. Korean Chem. Soc.*, 2008, **29**, 483.
- 44 S. Handa, K. Nagawa, Y. Sohtome, S. Matsunaga and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2008, **47**, 3230.
- 45 COLLECT Software, Nonius BV 1997–2001.
- 46 A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Crystallogr.*, 1994, **27**, 435.
- 47 Z. Otwinowski and W. Minor, *Methods in Enzymology*, ed. C. W. Carter, Jr and R. M. Sweet, Academic Press, New York, 1997, vol. 276, p. 307.
- 48 P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout and D. J. Watkin, *J. Appl. Crystallogr.*, 2003, **36**, 1487.
- 49 Stoe & Cie, IPDS software v 1.26, Stoe & Cie, Darmstadt, Germany, 1996.
- 50 G. M. Sheldrick, *Acta Crystallogr., Sect. A: Fundam. Crystallogr.*, 2008, **64**, 112.
- 51 I. J. Bruno, J. C. Cole, P. R. Edgington, M. K. Kessler, C. F. Macrae, P. McCabe, J. Pearson and R. Taylor, *Acta Crystallogr., Sect. B: Struct. Sci.*, 2002, **58**, 389.
- 52 S. Liu and C. Wolf, *Org. Lett.*, 2007, **10**, 1831.
- 53 T. Marcelli, R. N. S. van der Haas, J. H. van Maarseveen and H. Hiemstra, *Angew. Chem., Int. Ed.*, 2006, **45**, 929.
- 54 J. Bourguignon, G. Le Nard and G. Queguiner, *Can. J. Chem.*, 1985, **63**, 2354.
- 55 C. Gan, G. Lai, Z. Zhang, Z. Wang and M.-M. Zhou, *Tetrahedron: Asymmetry*, 2006, **17**, 725.
- 56 E. C. Constable, G. Zhang, C. E. Housecroft, M. Neuburger and S. Schaffner, *CrystEngComm*, 2009, **11**, 657.

- 57 H. Paulsson, A. Fischer and L. Kloo, *Acta Crystallogr., Sect. E*, 2004, **60**, m548.
- 58 N. P. Rath and E. M. Holt, *J. Chem. Soc., Chem. Commun.*, 1985, 665.
- 59 G. Hu and E. M. Holt, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1994, **50**, 1578.
- 60 A. K. Nurtaeva and E. M. Holt, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1998, **54**, 594.
- 61 A. S. Batsanov, Yu. T. Struchkov, L. Yu. Ukhin and N. A. Dolgoplova, *Inorg. Chim. Acta*, 1982, **63**, 17.
- 62 A. K. Nurtaeva, G. Hu and E. M. Holt, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1998, **54**, 597.