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FULL PAPER

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(3*S*,4*S*)-*N*-substituted-3,4-dihydroxypyrrolidines as ligands for the enantioselective Henry reaction

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The enantioselective Henry reaction is a very important and useful carbon–carbon bond forming reaction. The execution of this reaction requires the use of efficient chiral catalysts. In this work, in situ formed complexes of *N*-substituted dihydroxypyrrolidines, chiral ligands derived from L-tartaric acid and amines, were evaluated as catalysts in the enantioselective Henry reaction. The results showed that the nature of the *N*-substituent on the ligand significantly influences the outcome of the reaction. Best results were obtained using a Cu (II) complex of (3*S*,4*S*)-*N*-benzyl-3,4-dihydroxypyrrolidine, in the presence of DIPEA, for the reaction of aromatic aldehydes with nitromethane, at room temperature, originating products with *er* up to 92:8 (*R*:*S*) and conversions up to 96%. The interaction between the pyrrolidine ligand and the copper ion, in isopropanol, was followed by UV-vis spectrophotometry, showing a 1:1 stoichiometry and a binding constant of 4.4. The results obtained will contribute to the design and development of more efficient chiral catalysts for this type of reaction.

KEYWORDS
asymmetric catalysis, complex stoichiometry, Henry reaction, pyrrolidines

1 | INTRODUCTION

The Henry reaction allows the synthesis of β-nitro alcohols, precursors of several types of important compounds such as α-hydroxy ketones, carboxylic acids, amino alcohols and amino acids, among others.[1,2]

Although the Henry reaction is a classic C–C bond-forming reaction, the asymmetric version was only reported by Shibasaki et al.[3] Since then, various metal complexes of chiral ligands and chiral organocatalysts have been used in this reaction.[4,5] A variety of chiral ligands with different types of functionalities (amino alcohols, diols, diamines, salen, salan, amino phosphines, among others) have been reported in the literature.[1,6–12] The use of metals such as La, Mo, Zn, Co, Cr, Rh and with special emphasis Cu[13] has also been described.[5,14–18] Ligands containing a pyrrolidine moiety have been used in various catalytic reactions, with good results. Many of these ligands are based on L-proline, and this chiral precursor has been extensively explored in asymmetric catalysis, presenting high induction of chirality.[19–23] In the asymmetric Henry reaction, the use of proline derivatives and other pyrrolidine type chiral ligands, either as organocatalysts or as ligands in organometallic complexes, has also been reported, with promising results.[1,5,24–28]

Pyrrolidines derived from tartaric acid, which can be easily prepared by reaction with amines, have been less explored in the Henry reaction. Some mention has been made in literature to the use of tartaric acid derived catalysts for this reaction, although mostly regarding the use of TADDOL and its derivatives.[29–33]

In the continuation of our studies on the use of chiral pyrrolidines derived from tartaric acid for enantioselective transformations,[34–36] we decided to screen the potential of several dihydroxypyrrolidines in the Henry reaction. Most of the synthesized ligands have the advantage of being easily prepared in a synthetic sequence of only two steps, starting from inexpensive tartaric acid and amines.

2 | EXPERIMENTAL SECTION

2.1 | General

Commercially available compounds were used without further purification. All solvents were dried prior to use following standard procedures. Benzaldehyde was distilled prior to use and stored over 4 Å molecular sieves. Melting points were determined using a FALC melting point apparatus (open capillary method). Optical rotations were measured with an Optical Activity AA-5 polarimeter. NMR spectra were recorded at room temperature on a Bruker Avance III 400 MHz (100 MHz for ^{13}C). TMS was used as the internal standard and chemical shifts are given in ppm. Infrared spectra were recorded on an Agilent Technologies Cary 630 FTIR in the ATR mode. High-resolution mass spectra (HRMS) were obtained on a TOF VG Autospect M spectrometer with electrospray ionization (ESI). Conversions for the Henry reactions were determined by NMR. Enantiomeric ratios were determined by HPLC using an Agilent 1100 series instrument with a Chiralpack® IB column.

2.2 | General procedure for the synthesis of ligands 2d and 2e

2.2.1 | (3*R*,4*R*)-*N*-(2-tosylaminoethyl)-3,4-dihydroxy-2,5-dioxopyrrolidine 1d

To a suspension of tartaric acid (15 mmol, 2.25 g) in 25 ml of xylene, *N*-tosylethylenediamine (15 mmol, 3.21 g) was added, and the mixture was refluxed with stirring in a round bottom flask equipped with a Dean–Stark apparatus. The reaction was complete when the appropriate amount of water was collected (30 mmol, 0.54 ml). After cooling the reaction mixture, the precipitated product was filtered and recrystallized in acetone/hexane to give a beige solid.

Yield: 54%. $[\alpha]_D^{20} = +65$ (*c*1, EtOH); m.p. = 133–134°C. IR (cm^{-1}): 3274 (OH), 1713 (C=O), 1688 (C=O), 1331 (SO_2), 1159 (N–SO_2), 1065 (C–O), 816 (*p*-Ar). ^1H NMR (DMSO-*d6*), δ (ppm): 2.39 (s, 3*H*, CH_3); 2.87 (q, 2*H*, CH_2, J = 6.4 Hz); 3.41 (t, 2*H*, CH_2, J = 6.4 Hz); 4.32 (d, 2*H*, CH, J = 4.0 Hz); 6.27 (approx. d, 2*H*, OH, J = 4.0 Hz); 7.40 (d, 2*H*, H–Ar, J = 8.2 Hz); 7.65 (d, 2H, H–Ar, J = 8.2 Hz); 7.75 (t, 1*H*, NH, J = 6.4 Hz). ^{13}C NMR (DMSO-*d6*), δ (ppm): 20.9 (CH_3), 37.8 (CH_2), 39.4 (CH_2), 74.2 (CH), 126.4 (C–Ar), 129.7 (C–Ar), 137.4 (C–Ar), 142.7 (C–Ar), 174.6 (CO). HRMS (ESI): calculated for $C_{13}H_{17}N_2O_6S$ $[M + H]^+$ 329.0802, found 329.0805.

2.2.2 | (3*S*,4*S*)-*N*-(2-tosylaminoethyl)-3,4-dihydroxypyrrolidine 2d

In a round bottom flask, cooled in an ice bath, lithium aluminum hydride (11.5 mmol, 0.44 g) was slowly added to (3*R*,4*R*)-*N*-(2-tosylaminoethyl)-3,4-dihydroxy-2,5-dioxopyrrolidine (5 mmol, 1.64 g) in diethyl ether (25 ml). The mixture was then refluxed for 48 h. After cooling, in an ice bath, ethyl acetate was slowly added to the reaction mixture, followed sequentially by water (0.5 ml), NaOH, 15% (0.5 ml) and water again (1.5 ml). The resulting mixture was stirred for 1 h, filtered with celite and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the resulting oil was purified by column chromatography using silica gel and CH_2Cl_2/MeOH (90:10) as eluent.

Yield: 18%. $[\alpha]_D^{20} = +11.5$ (*c*1.3, EtOH); m.p: 88°C (degradation). IR (cm^{-1}): 3156 (OH), 1324 (SO_2), 1152 (N–SO_2), 1080 (C–O), 814 (*p*-Ar). ^1H NMR (DMSO-*d6*), δ (ppm): 2.22 (dd, 2*H*, CH_2, J = 3.6 Hz, 9.6 Hz); 2.32–2.41 (m, 2*H*, CH_2); 2.39 (s, 3*H*, CH_3); 2.68 (dd, 2*H*, CH_2, J = 5.6 Hz, 9.6 Hz); 2.76 (t, 2*H*, CH_2, J = 6.8 Hz); 3.76 (approx. d, 2*H*, CH, J = 4.4 Hz); 4.79 (d, 2*H*, OH, J = 4.8 Hz); 7.40 (d, 2*H*, H–Ar, J = 8.0 Hz); 7.69 (d, 2*H*, H–Ar, J = 8.0 Hz). ^{13}C NMR (DMSO-*d6*), δ (ppm): 21.5 (CH_3), 40.7 (CH_2), 54.6 (CH_2), 59.8 (CH_2), 77.7 (CH), 127.1 (C–Ar), 129.8 (C–Ar), 136.6 (C–Ar), 143.5 (C–Ar). HRMS (ESI): calculated for $C_{13}H_{21}N_2O_4S$ $[M + H]^+$ 301.1217, found 301.1222.

2.2.3 | (3*S*,4*S*)-*N*-benzyl-3,4-diacetoxypyrrolidine 2f

To acetic anhydride (25 mmol, 2.36 ml), compound **2a** (10 mmol, 1.93 g) and sodium acetate trihydrate (10 mol%, 1 mmol, 0.14 g) were added. The mixture was reacted at room temperature for 1 h and then diluted with ethyl acetate (10 ml) and washed twice with a saturated solution of $NaHCO_3$. The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The product, an oil, was purified by column chromatography using silica gel and EtOAc/hexane (1:1) as eluent.

Yield: 85%. $[\alpha]_D^{20} = +35.7$ (c1.1, CH_2Cl_2). IR (cm^{-1}): 2798 (CH), 1734 (C=O), 1073 (C–O), 745 (Ar). ^1H NMR ($CDCl_3$), δ (ppm): 2.06 (s, 6*H*, CH_3); 2.55 (dd, 2*H*, CH_2, J = 4.0 Hz, 10.8 Hz); 3.08 (dd, 2*H*, CH_2, J = 5.6 Hz, 10.8 Hz); 3.62 (d, 1*H*, CH_2, J = 13.0 Hz); 3.69 (d, 1*H*, CH_2, J = 13.0 Hz); 5.12(dd, 2*H*, CH, J = 4 Hz, 5.6 Hz); 7.25–7.35 (m, 5*H*, H–Ar). ^{13}C NMR ($CDCl_3$), δ (ppm): 21.0 (CH_3), 58.1 (CH_2), 59.7 (CH_2), 77.7 (CH), 127.3 (C–Ar), 128.4 (C–Ar), 128.9 (C–Ar), 137.5 (C–Ar), 170.4 (CO). HRMS (ESI): calculated for $C_{15}H_{20}NO_4$ $[M + H]^+$ 278.1387, found 278.1392.

2.2.4 | (3*S*,4*S*)-diacetoxypyrrolidine 2g

In a round-bottom flask compound **2f** (10 mmol, 2.77 g), ammonium formate (20 mmol, 1.26 g) and Pd/C 10% (0.3 g) in methanol (100 ml) were added. The mixture was refluxed for 1 h, cooled to room temperature, filtered with celite and washed several times with methanol. After evaporation of the solvent under reduced pressure, the product was obtained as an oil and was used directly in the synthesis of **2h**.

Yield: 98%. ^1H NMR ($CDCl_3$), δ (ppm): 2.08 (s, 6*H*, CH_3); 2.56 (dd, 2*H*, CH_2, J = 4.2 Hz, 10.4 Hz); 3.12 (dd, 2*H*, CH_2, J = 5.8 Hz, 10.4 Hz); 5.12 (dd, 2*H*, CH, J = 4.2 Hz, 5.8 Hz).

2.2.5 | (3*S*,4*S*)-*N*-benzoyl-3,4-diacetoxypyrrolidine 2h

In a two-necked round bottom flask, cooled in an ice bath, compound **2g** (9 mmol, 1.68 g) and triethylamine (10.8 mmol, 1.5 ml) in dichloromethane (25 ml) were added. In inert atmosphere and via syringe, benzoyl chloride (10.8 mmol, 1.25 ml) was slowly added and then the reaction mixture was stirred for 4 h, at room temperature. The mixture was extracted twice with water, the organic phase was washed with a saturated solution of $NaHCO_3$, dried with anhydrous Na_2SO_4, filtered and the solvent was evaporated. The product, an oil, was purified by column chromatography using silica gel and EtOAc/hexane (1:1) as eluent.

Yield: 70%. $[\alpha]_D^{20} = -4.10$ (c4.9, CH_2Cl_2). IR (cm^{-1}): 1741 (C=O), 1628 (C=O), 1060 (C–O), 731 (Ar). ^1H NMR ($CDCl_3$), δ (ppm): δ 2.05 (s, 3*H*, CH_3); 2.12 (s, 3*H*, CH_3); 3.51 (approx. d, 1*H*, CH_2, J = 12.4 Hz); 3.80 (approx. d, 1*H*, CH_2, J = 14.0 Hz); 3.91 (dd, 1*H*, CH_2, J = 4.0 Hz, 12.4 Hz); 4.06 (dd, 1H, CH_2, J = 4.4 Hz, 14.0 Hz); 5.08–5.12 (m, 1*H*, CH); 5.23–5.32 (m, 1*H*, CH); 7.27–7.54 (m, 5*H*, H–Ar). ^{13}C NMR ($CDCl_3$), δ (ppm): 20.8 (CH_3), 20.9 (CH_3), 50.4 (CH_2), 52.9 (CH_2), 73.7 (CH), 75.0 (CH), 127.3(C–Ar), 128.5 (C–Ar), 130.5 (C–Ar), 135.8 (C–Ar), 169.6 (CO), 169.7 (CO), 170.1 (CO). HRMS (ESI): calculated for $C_{15}H_{18}NO_5$ $[M + H]^+$ 292.1179, found 292.1178.

2.2.6 | (3*S*,4*S*)-*N*-benzoyl-3,4-dihydroxypyrrolidine 2e

Compound **2h** (5 mmol, 1.46 g) and NaOH (10 mmol, 0.40 g), dissolved in water (25 ml), were stirred at room temperature for 3 h. The reaction mixture was extracted several times with $CHCl_3$, dried with anhydrous Na_2SO_4, filtered and the solvent was evaporated.

Yield: 74%. ^1H NMR ($CDCl_3$), δ (ppm): 3.25 (approx. d, 1*H*, CH_2, J = 11.4 Hz); 3.53 (approx. d, 1*H*, CH_2, J = 13.0 Hz); 3.67 (dd, 1*H*, CH_2, J = 4.0 Hz, 11.4 Hz); 3.82 (dd, 1*H*, CH_2, J = 4.0 Hz, 13.0 Hz); 4.02 (sl, 1*H*, CH); 4.14 (sl, 1*H*, CH); 7.19–7.38 (m, 5*H*, H–Ar).

2.3 | General procedure for the addition of nitromethane to aldehydes

Chiral ligand (0.08 mmol) and solvent (8 ml) were stirred in a round bottom flask, until ligand dissolution was complete. Then the metal salt (0.08 mmol) was added and allowed to stir for 2 h, at room temperature (ultrasound was used for better solubilization when the solvent was toluene). The substrate (0.8 mmol) and nitromethane (44.8 mmol) were then added, and the mixture was allowed to stir for 10 min. The base (0.04 mmol) was then added, and the reaction mixture stirred for 48 h at room temperature.

The solvent was removed under reduced pressure and the residue was purified by column chromatography using silica gel and ethyl acetate/hexane mixtures as eluent.

The enantiomeric ratio of the products was determined by HPLC analysis (254 nm), using hexane/isopropanol mixtures as eluent. The absolute configurations of the products were assigned by comparison to literature values and by the sign of the optical rotation of the products.[37,38]

The HPLC conditions and retention times for the different products of the Henry reaction are 1-phenyl-2-nitroethanol, hexane:*i*PrOH (90:10), 1 ml/min, t_R = 5.8 and 6.5 min; 1-(2-nitrophenyl)-2-nitroethanol, hexane:*i*PrOH (90:10), 1 ml/min, t_R = 8.1 and 8.7 min; 1-(3-nitrophenyl)-2-nitroethanol, hexane:*i*PrOH (90:10), 1 ml/min, t_R = 12.5 and 14.1 min; 1-(4-nitrophenyl)-2-nitroethanol, hexane:*i*PrOH (85:15), 0.8 ml/min t_R = 10.4 and 12.0 min; 1-(2-chlorophenyl)-2-nitroethanol, hexane:*i*PrOH (90:10), 1 ml/min, t_R = 17.6 and 18.9 min; 1-(4-chlorophenyl)-2-nitroethanol, hexane:*i*PrOH (85:15), 0.8 ml/min t_R = 9.3 and 11.4 min; 1-(2-methoxyphenyl)-2-nitroethanol, hexane:*i*PrOH (90:10), 0.8 ml/min t_R = 6.7 and 7.2 min; 1-(3-methoxyphenyl)-2-nitroethanol, hexane:*i*PrOH (90:10), 1 ml/min t_R = 8.1 and 9.0 min; 1-(2-methylphenyl)-2-nitroethanol, hexane:*i*PrOH (90:10), 1 ml/min t_R = 4.7 and 5.6 min; 1-(3-methylphenyl)-2-nitroethanol, hexane:*i*PrOH (90:10), 1 ml/min t_R = 4.9 and 5.4 min.

2.4 | UV-visible spectroscopy measurements

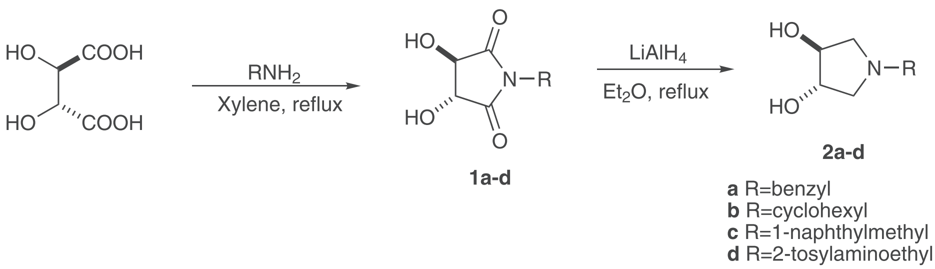
The UV-visible spectra of solutions of Cu (II), in the absence and presence of the pyrrolidine, were recorded on a Shimadzu 2450 UV-vis spectrophotometer. For Job's method of continuous variation,[39] the total concentration of the two species is kept constant and equal to 4 mM. For the determination of the binding constant, a titration of a 4 mM Cu (II) solution was carried out by using a **2a** solution. The concentration of the latter varied between 0.5 and 8 mM. All solutions were prepared by using isopropanol as solvent.

3 | RESULTS AND DISCUSSION

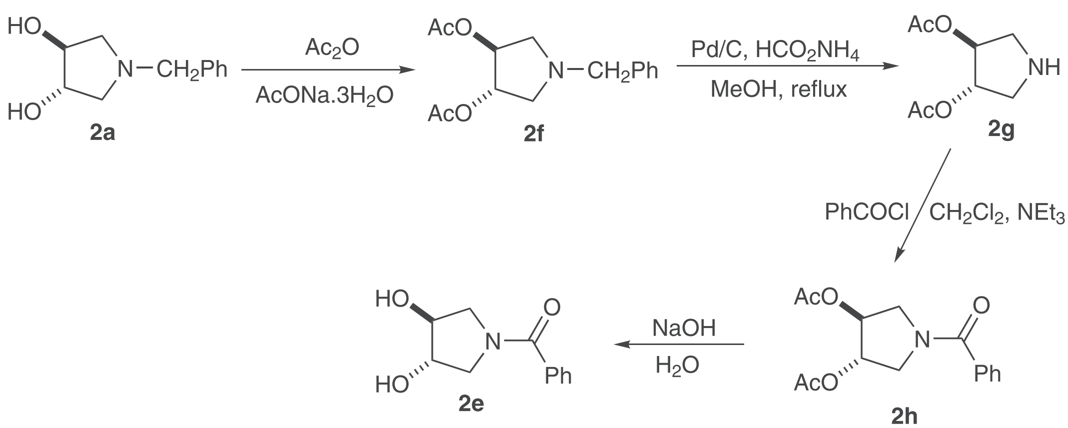
3.1 | Ligand synthesis

Ligands **2a-c** were prepared according to previously described procedures.[34,40,41] Dihydroxydioxopyrrolidines (**1a-c**) were synthesized in good yields (62%–92%), through the condensation of tartaric acid with several amines (benzylamine, cyclohexylamine and naphthymethylamine) in refluxing xylene, using a Dean–Stark apparatus (Scheme 1). Reduction of **1a-c** with $LiAlH_4$, using diethyl ether as solvent, allowed the synthesis of the dihydroxypyrrolidines **2a-c** in moderate yields (45%–48%), after a 48 h reflux. Dihydroxypyrrolidine **2d** was synthesized using a similar procedure, starting from *N*-tosylethylenediamine and tartaric acid (**1d** 54% yield, **2d** 18% yield).

Ligand **2e,** already described by Siedlecka et al.,[42] was prepared using a slightly different strategy, starting from **2a**, Scheme 2. Briefly, **2a** was acetylated with acetic anhydride in the presence of sodium acetate, at room temperature, to give **2f** in quantitative yield. **2g** was prepared in 94% yield by hydrogenolysis of the benzyl group with ammonium formate and Pd/C 10%, in methanol reflux. Reaction of **2g** with benzoyl chloride, in the presence of NEt_3, gave **2h** in 70% yield. Finally, hydrolysis of the acetate group with aqueous NaOH allowed the synthesis of ligand **2e** (74% yield).



SCHEME 1 Pyrrolidine synthesis



SCHEME 2 Synthesis of *N*-benzoylpyrrolidine

3.2 | Catalytic studies

In the initial experiments, ligand **2a** was used to optimize several reaction parameters. The ligand was reacted *in situ* with Cu $(OAc)_2 \cdot H_2O$ to form the catalyst, and subsequently tested in the enantioselective Henry reaction between benzaldehyde and nitromethane, at room temperature for 48 h, using isopropanol as solvent, and Na_2CO_3 as additive (no product was observed in the absence of a base). Lower temperatures (0°C) resulted in lower conversions and *er* (84% and 81.5:18.5, respectively). For lower reaction times, less than 48 h, a significant amount of reagent was detected by TLC. Using 10 mol% of the complex, in a 1:1 ligand:metal stoichiometry, 90% conversion of the substrate was obtained, with 86% of chiral nitroaldol product **3a** and 14% of nitroalkene **3b**, resulting from the elimination of a water molecule (Scheme 3).

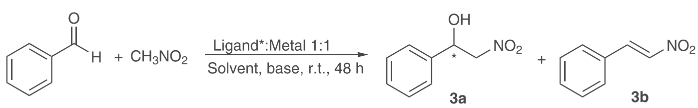
An enantiomeric ratio (*er*) of only 54.5:45.5 (*R*:*S*) was obtained using these conditions. With 15 or 20 mol% of catalyst, conversions were higher (96 and 97%, respectively) but percentages of the chiral product were lower (72% and 46%, respectively). Using 5 mol% of catalyst a lower *er* 51.5:48.5 (*R*:*S*) was obtained. Thus, it was decided to use 10 mol% of catalyst to proceed the studies.

The solvent is another parameter that can influence the outcome of the Henry reaction. The use of polar and apolar solvents is mentioned in the literature, although polar protic solvents such as alcohols usually give better conversions and *er*.[43–46] Therefore, several alcohols were tested as solvents for the reaction and conversions higher than 96% were obtained in all cases. However, low *er* resulted with all the alcohols tested. Polar aprotic solvents such as dichloromethane, diethyl ether and THF gave lower conversions, but higher *er*. Toluene, an apolar solvent, gave the best results, with almost complete conversion and an *er* of 87:13 (*R*:*S*), Table 1. This same trend, in which aromatic solvents lead to better induction of chirality, has been previously observed.[6,47–49]

The use of different metal salts for the Henry reaction is reported. Thus, copper, zinc, nickel and cobalt salts were complexed with ligand **2a** and tested in the reaction of benzaldehyde with nitromethane. The results are summarized in Table 2.

Good conversions were obtained with all the metal salts but, in some cases, the main product was the nitroalkene, instead of the nitroaldol. Better results were obtained using Cu $(OAc)_2.H_2O$ as the metal salt, as has been previously referred.[7,13,50,51]

Alkaline additives can be used in the Henry reaction to deprotonate nitromethane, forming the corresponding nitronate and thus improving the outcome of the reaction. Bases such as carbonates and amines are widely used.[10,11,49,52] Accordingly, several bases (5 mol% with respect to the aldehyde) were screened as additives for the Henry reaction, as reported in Table 3. Except for NEt_3, very good conversions were obtained with all bases (greater than 92%). Although bases can also deprotonate the nitroaldol product and thus favor the formation of the nitroalkene, this did not occur with those studied. With regard to *er*, the best results were obtained using



SCHEME 3 Henry reaction products

TABLE 1 Solvent effect on the Henry reaction[a]

Solvent	Conversion (%)[b]	Chiral product (%)[b]	*er* (*R*:*S*)[c]
MeOH	97	89	54:46
EtOH	96	95	51:49
^{i}PrOH	97	81	56:44
BuOH	97	81	59:41
CH_2Cl_2	47	93	n.d.
Et_2O	78	90	86.5:13.5
THF	84	92	68:32
Toluene	>99	91	87:13

[a]Benzaldehyde (0.8 mmol), ligand **2.2a** (0.08 mmol), Cu $(OAc)_2.H_2O$ (0.08 mmol), CH_3NO_2 (44.8 mmol), Na_2CO_3 (0.04 mmol), solvent (8 ml), 48 h.
[b]Determined by ^{1}H NMR.
[c]Determined by chiral HPLC.

TABLE 2 Metal salt effect on the Henry reaction[a]

Metal	Conversion (%)[b]	Chiral product (%)[b]	*er* (*R*:*S*)[c]
Cu $(OAc)_2.H_2O$	>99	91	87:13
CuCl	>99	>99	65:35
$CuCl_2.2H_2O$	98	30	n.d.
Zn $(OTf)_2$	96	75	50:50
Zn $(OAc)_2.2H_2O$	95	87	46.5:53.5
Ni $(OAc)_2.4H_2O$	>99	70	47.5:52.5
Co $(OAc)_2.4H_2O$	98	10	n.d.

[a]Benzaldehyde (0.8 mmol), ligand **2.2a** (0.08 mmol), metal salt (0.08 mmol), CH_3NO_2 (44.8 mmol), Na_2CO_3 (0.04 mmol), toluene (8 mL), 48 h.
[b]Determined by ^{1}H NMR.
[c]Determined by chiral HPLC.

TABLE 3 Base effect on the Henry reaction[a]

Base	Conversion (%)[b]	Chiral product (%)[b]	*er* (*R*:*S*)[c]
DABCO[d]	99	93	85.5:14.5
DBU[e]	94	95	72.5:27.5
NEt_3	78	96	82:18
DIPEA[f]	92	91	89.5:10.5
Na_2CO_3	>99	91	87:13
Cs_2CO_3	>99	95	83:17

[a]Benzaldehyde (0.8 mmol), ligand **2.2a** (0.08 mmol), Cu $(OAc)_2.H_2O$ (0.08 mmol), CH_3NO_2 (44.8 mmol), base (0.04 mmol), toluene (8 mL), 48 h.
[b]Determined by ^{1}H NMR.
[c]Determined by chiral HPLC.
[d]1,4-diazabicyclo[2.2.2]octane.
[e]1,8-diazabicyclo[5.4.0]undec-7-ene.
[f]Diisopropylethylamine.

diisopropylethylamine (DIPEA), albeit the conversion is less than that obtained with Na_2CO_3.

In an attempt to improve the *er*, using DIPEA as additive, the reaction temperature was lowered to 0°C. Under these reaction conditions, a lower conversion was obtained (84%) and the *er* decreased to 82.5:17.5 (*R*:*S*).

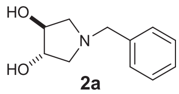
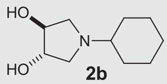
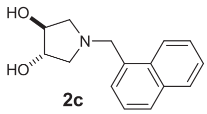
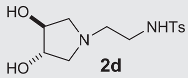
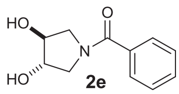
Using the optimized reaction conditions, the other ligands prepared were screened for their catalytic activity in the Henry reaction (Table 4). Comparing ligands **2b-c** with **2a**, it can be concluded that the presence of a naphthylmethyl or a cyclohexyl group on the nitrogen of the hydroxypyrrolidine slightly decreases the *er* of the reaction.

Ligand **2e** was prepared aiming to study the influence of the presence of a more sterically demanding and electron attracting benzoyl group on the nitrogen atom of the ligand. It was observed that the presence of this group decreases the conversion of the reaction but, most importantly, it has a drastic effect on the *er*. This may be due to the fact that the carbonyl group is more sterically demanding than the methylene group of ligand **2a** and this may lead to high steric hindrance in the transition state. Another feature that may explain this marked difference in the *er* is that the carbonyl group can remove electron density from the nitrogen atom, and this may affect the coordination to the metal. These two aspects can thus affect the relative energies of the transition states in the Henry reaction and lead to products with lower selectivity.

Ligand **2d**, unlike the other ligands, can coordinate with copper in a tridentate manner. Because references are made in the literature to the use of tridentate ligands with good results, we thought that it would be interesting to synthesize and test this ligand. As can be seen from the results in Table 4, ligand **2d** gave low conversion and a racemic product.

Using our most efficient ligand **2a**, the scope of the reaction was then extended to other aromatic substrates and the results are summarized in Table 5. In general, aromatic substrates with electron-withdrawing groups presented better conversions than those containing electron-donating groups. On the contrary, better *er* were obtained with aromatic substrates containing electron-donating groups.

TABLE 4 Henry reaction using L-tartaric acid derived ligands[a]

Ligand	Conversion (%)[b]	Chiral product (%)[b]	*er* (*R*:*S*)[c]
 2a	92	91	89.5:10.5
 2b	81	84	83: 17
 2c	>99	94	82.5:17.5
 2d	77	72	50:50
 2e	78	92	51:49

[a]Benzaldehyde (0.8 mmol), ligand (0.08 mmol), Cu $(OAc)_2.H_2O$ (0.08 mmol), CH_3NO_2 (44.8 mmol), DIPEA (0.04 mmol), toluene (8 mL), 48 h.
[b]Determined by ^{1}H NMR.
[c]Determined by chiral HPLC.

TABLE 5 Substrate effect on the Henry reaction[a]

Aldehyde	Conversion (%)[b]	*er* (*R*:*S*)[c]
Benzaldehyde	92	89.5:10.5
2-Nitrobenzaldehyde	82	57:43
3-Nitrobenzaldehyde	69	58:42
4-Nitrobenzaldehyde	87	63.5:36.5
2-Chlorobenzaldehyde	96	76.5:23.5
4-Chlorobenzaldehyde	55	75.5:24.5
2-Methoxybenzaldehyde	53	92:8
3-Methoxybenzaldehyde	27	86:14
4-Methoxybenzaldehyde	10	n.d.
2-Methylbenzaldehyde	49	89.5:10.5
3-Methylbenzaldehyde	42	82.5:17.5

[a]Benzaldehyde (0.8 mmol), ligand **2.2a** (0.08 mmol), Cu $(OAc)_2.H_2O$ (0.08 mmol), CH_3NO_2 (44.8 mmol), DIPEA (0.04 mmol), Toluene (8 mL), 48 h.
[b]Determined by ^{1}H NMR.
[c]Determined by chiral HPLC.

Our best result was obtained using 2-methoxybenzaldehyde as substrate, giving the product with an *er* of 92:8 (*R*:*S*).

3.3 | Determination of the pyrrolidine-copper complex stoichiometry

In order to get insight on how our best ligand, pyrrolidine **2a**, coordinates with copper to form the catalytically active species, a different set of experiments were carried out. Since the Cu (II) solution shows a well-defined UV–visible spectrum, with a maximum at 702 nm, the method of continuous variation was applied to evaluate the stoichiometry of the interaction. It can be seen from the analysis of Figure 1b that this method shows a maximum at 0.46, suggesting a 1:1 stoichiometry between **2a** and Cu $(OAc)_2$. A possible structure for this complex is presented in Figure 2. It can also be seen that Job's plot does not show a reverse V-shape, but instead a Gaussian-like trend. Such a behavior has been discussed elsewhere[53] and suggests a lower binding constant between the Cu (II) and **2a**. Based on this stoichiometry, and taking into account the suggested catalytic cycle of similar compounds,[46] the following equation is suggested:

$$\mathrm{Cu\,(OAc)_2} + \mathbf{2a-H} \rightleftarrows \mathrm{Cu\,(OAc)}(\mathbf{2a}) + \mathrm{HOAc} \qquad (1)$$

For the sake of simplicity, we have highlighted the hydrogen atom of the pyrrolidine, in the equation, which is deprotonated in the presence of copper acetate to form the complex Cu (OAc)(**2a**) (Figure 2).

Based on equation (1), and considering the [Cu (OAc)(**2a**)] = [HOAc], the corresponding binding constant, *K*, can be written as

$$K = [Cu(OAc)(2a)]^2 / ([2a][Cu(OAc)_2]) \qquad (2)$$

The variation of the experimental absorbance, ΔA, defined as a difference of the absorbance of the Cu (II) solution in the presence and absence of pyrrolidine

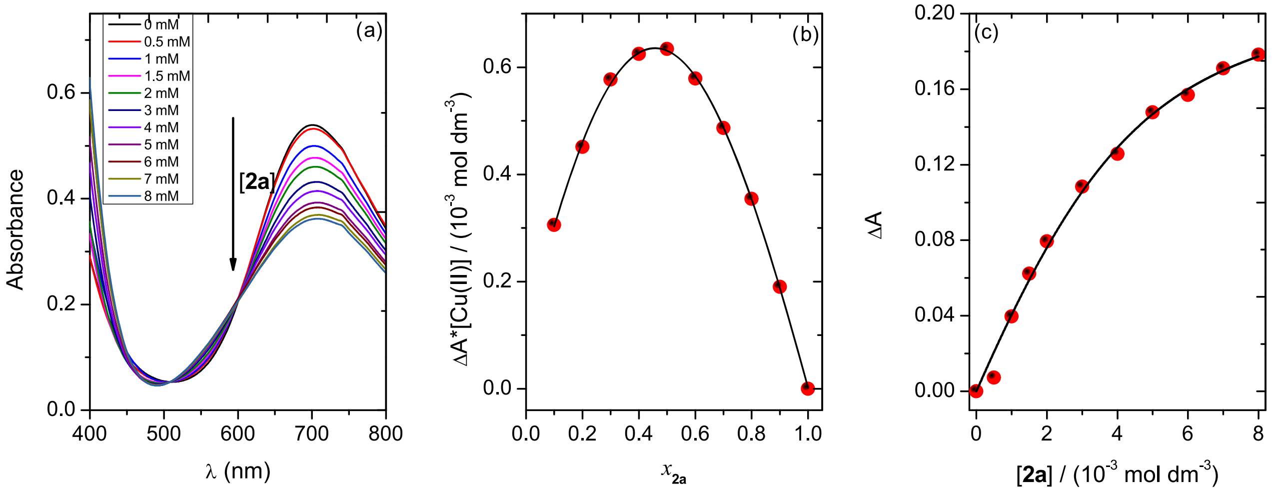


FIGURE 1 (a) UV-visible spectra of 4 mM Cu (II) solutions in the presence of increasing concentrations of **2a**; (b) Job's plot for **2a** and Cu (II) mixtures at different **2a** molar fractions; and (c) effect of **2a** concentration on the absorbance of a Cu (II) solution, at 702 nm (Figure 1a). Solid lines in b and c were obtained by fitting the experimental data to a Gram–Charlier peak function[55] and to Equations 3 and 4, respectively

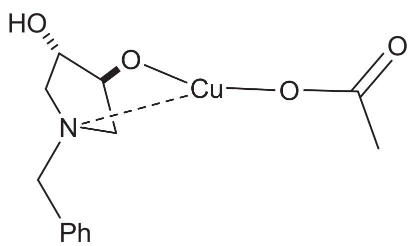


FIGURE 2 Possible structure of the **2a**: copper 1:1 complex

2a, is dependent on the concentration of the complex, as described in Equation 3:

$$\Delta A = \frac{\Delta A_{Cu(OAc)(2a)}}{[Cu(OAc)_2]_T}[Cu(OAc)(2a)] \quad (3)$$

where $[Cu\ (OAc)_2]_T$ is the total concentration of Cu (II) in solution and $\Delta A_{Cu(OAc)(2a)}$ corresponds to the change of absorbance due to the complex; it should be noted that the absorbance has a contribution of free and complexed Cu (II) species.

From the mass balances for Equation 1 and after some algebraic manipulation,[53] the concentration of the complex can be computed from the following equation:

$$[Cu(OAc)(2a)] = \frac{([Cu(OAc)_2]_T + [2a]_T) - \left(([Cu(OAc)_2]_T + [2a]_T)^2 - 4\frac{K-1}{K}[Cu(OAc)_2]_T[2a]_T\right)^{1/2}}{2\frac{K-1}{K}} \quad (4)$$

Figure 1c shows the fitting of Equations 3 and 4 to the experimental ΔA, using a non-linear least-squares algorithm. The computed fitting parameters are: $K = 4.4$ ($\pm$1.9), $\Delta A_{Cu(OAc)(2a)} = 0.20$ ($\pm$0.01), for a determination coefficient of 0.9967 and a $\chi^2 = 1.2 \times 10^{-5}$. These results show that, under the experimental conditions used (i.e., in a 4 mM equimolar mixture of Cu $(OAc)_2$ and **2a**) 39% of the ligand remains uncomplexed. This is in close agreement with the shape of Job's plot as well as with the absence of a clear plateau of DA as a function of [**2a**] in Figure 1c. It should be noticed that stability for Cu (II)-ligand interaction was measured in a low dielectric constant solvent, which justified the magnitude of the binding constant.[54]

4 | CONCLUSIONS

Several metal complexes of chiral *N*-substituted dihydroxypyrrolidines derived from L-tartaric acid and amines were prepared, in short and simple synthetic sequences, and evaluated in the enantioselective Henry reaction. It was observed that the nature of the substituent on the pyrrolidine nitrogen significantly influences the outcome of the reaction. Under optimized reaction conditions and using a Cu (II) complex of (3*S*,4*S*)-*N*-benzyl-3,4-dihydroxypyrrolidine, conversions up to 96% and *er* up to 92:8 (*R*:*S*) were obtained for the reaction of aromatic aldehydes with nitromethane, in the presence of DIPEA, at room temperature. The stability constant for Cu (II)-(3*S*,4*S*)-*N*-benzyl-3,4-dihydroxypyrrolidine was additionally evaluated by UV–vis spectroscopy and has been computed as equal to 4.4, considering a 1:1 stoichiometry.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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AUTHOR CONTRIBUTIONS

Márcia Rénio: Investigation. **Francisco Sousa:** Investigation. **Nélia Tavares:** Investigation. **Artur Valente:** Conceptualization; supervision. **M. Elisa da Silva Serra:** Conceptualization; supervision. **Dina Murtinho:** Conceptualization; supervision.

CONFLICT OF INTEREST

There are no competing interests to declare.

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