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# Enantioselective Henry Reaction Catalyzed by Copper(II) Complex of Bis(*trans*-cyclohexane-1,2-diamine)-Based Ligand

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**Abstract:** Copper(II) complex of the ligand possessing two enantiomerically pure *trans*-cyclohexane-1,2-diamine units proved to be an efficient catalyst for the enantioselective Henry reaction of aromatic aldehydes with nitromethane. The effect of various reaction conditions on yield and enantioselectivity of the Henry reaction was studied. The results suggest that only one cyclohexane-1,2-diamine unit is involved in catalysis of the Henry reaction.

**Keywords:** Henry reaction; enantioselective catalysis; *trans*-cyclohexane-1,2-diamine; copper(II) complexes



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## 1. Introduction

Base-catalyzed nucleophilic addition of nitroalkane to carbonyl compound is an important carbon–carbon bond-forming reaction [1–3]. The reaction is named Henry reaction according to its discoverer [4] and because of its similarity with the aldol reaction it is also referred as the nitroaldol reaction. A significant feature of the Henry reaction is a possibility to conduct the reaction enantio- or diastereoselectively. Chiral products of the Henry reaction, 2-nitroalcohols, are important intermediates in syntheses of many biologically active compounds, such as antiasthmatic drug (*R*)-salmeterol [5], antibiotics L-acosamine [6] and bestatin [7], or fungicide (*S*)-spirobrassinin [8]. In the past, development of the field of stereoselective Henry reaction had been rather slow [9]. One major obstacle is that the reaction components, nitroalkane and a carbonyl compound, lack of suitable points for attachment of chiral auxiliaries. In addition, the reversible nature of the reaction and relatively easy racemization at the stereogenic center (located at the α-position to the nitro group) have hampered the progress in stereocontrol of the Henry reaction. In general, enantioselectivity of the reaction can be controlled by chirality of a substrate, chiral auxiliary, or catalyst. Among these approaches, employment of the chiral catalyst is highly advantageous since the usually expensive and heavily accessible enantiomerically pure compound is used in less than stoichiometric amount.

The first catalyst-controlled enantioselective Henry reaction was reported by Shibasaki [10] in 1992. A large number of catalysts capable of catalyzing the nitroaldol reaction enantioselectively has been developed since then, including both metal catalysts [11] and organocatalysts [12]. For example, copper(II) complexes of bis(oxazolidine) ligands [13], lanthanide complexes of 1,1′-binaphthalene-2,2′-diol derivatives [14], dinuclear zinc(II) complexes of $C_2$-symmetric alcohols [15], and copper(II) complexes of chiral ethane-1,2-diamine derivatives [16,17] were successfully used in the metal-based catalysis. Chiral guanidines [18], bis(thioureas) [19,20] or cinchona alkaloids [21] can serve as examples of efficient organocatalysts.

Recently, mononuclear copper complexes of secondary amines derived from enantiomerically pure *trans*-cyclohexane-1,2-diamine have been reported to achieve modest to excellent enantioselectivities in the Henry reaction [22–30]. Zhang et al. [31] have developed efficient binuclear copper(II) complex of the $C_2$-symmetric ligand, in which two

chiral β-amino alcohols are connected at the 1,4-positions to the central benzene ring. Their binuclear complex exhibited significantly higher enantioselectivities over the mononuclear one. Based on these published results, we decided to prepare ligand **1** possessing two *trans*-cyclohexane-1,2-diamine units attached to the central benzene unit (Figure 1) and study the effect of the second metal center in the binuclear complex on catalytic activity and enantioselectivity of the Henry reaction.

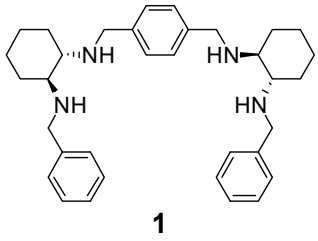
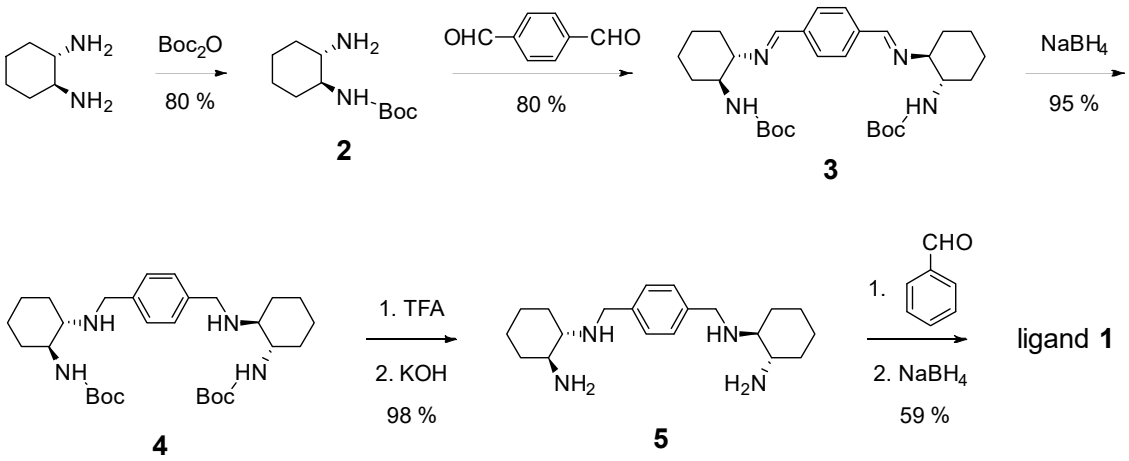



**Figure 1.** Structure of ligand **1**.

## 2. Results

### *2.1. Synthesis of Ligand 1*

Preparation of ligand **1** was previously published by Bellemin-Laponnaz et al. [32] and we used the same synthetic strategy with some experimental modifications. The synthesis started from (1*S*,2*S*)-*trans*-cyclohexane-1,2-diamine, which was first monoprotected with the *tert*-butoxycarbonyl group [33]. Carbamate **2** was condensed with terephthaldehyde, and the resulting Schiff base **3** was reduced with $NaBH_4$. The obtained amine **4** was deprotected and tetraamine **5** was condensed with two molar equivalents of benzaldehyde to give Schiff base, whose two imine double bonds were finally reduced with $NaBH_4$ giving ligand **1** in 36% overall yield (Scheme 1).




**Scheme 1.** Synthesis of ligand **1**.

Contrary to original authors [32], we had to isolate and carefully purify all intermediates in the reaction sequence. If crude intermediates were used in subsequent steps, we were not able to obtain ligand **1** in sufficient purity.

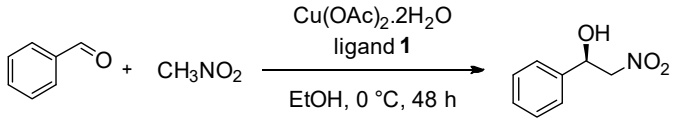
### *2.2. Catalytic Studies of the Henry Reaction*

The reaction of benzaldehyde with 10 molar equivalents of nitromethane was selected for initial experiments to elucidate the catalytic activity of the copper(II) complex of ligand **1** in the Henry reaction. The copper(II) complexes were generated in situ by mixing the appropriate amount of ligand and copper(II) salt prior to the Henry reaction. After the complex formation, the solution was cooled to 0 °C and benzaldehyde and nitromethane were added. At the end of the reaction, the product was isolated by column

chromatography and the enantiomer ratio was determined by HPLC on a column with chiral stationary phase. Isolated yield is reported throughout the article.

In the first experiments, the effect of ligand: copper(II) ratio on enantioselectivity of the reaction was studied using $Cu(OAc)_2 \cdot 2H_2O$ as a source of copper(II) ions and ethanol as a solvent (Table 1).

**Table 1.** Effect of molar ratios ligand **1**: copper(II) acetate: benzaldehyde on the reaction of benzaldehyde with nitromethane [a].



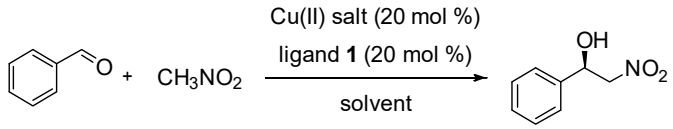

| Entry | Ligand 1 [molar %] [b] | $Cu(OAc)_2 \cdot 2H_2O$ [molar %] [b] | Molar Ratio Ligand 1:Cu(II) | Yield [c] [%] | e.e. [d] [%] |
|---|---|---|---|---|---|
| 1 | 20 | - | - | - | - |
| 2 | - | 20 | - | - | - |
| 3 | 20 | 20 | 1:1 | 71 | 91 |
| 4 | 10 | 20 | 1:2 | 39 | 86 |
| 5 | 2 | 20 | 1:10 | 23 | 87 |
| 6 | 20 | 200 | 1:10 | 69 | 84 |
| 7 | 5 | 5 | 1:1 | 40 | 89 |
| 8 | 10 | 10 | 1:1 | 46 | 88 |

[a] Reaction conditions: benzaldehyde (0.2 mmol), nitromethane (2 mmol), ethanol (2.0 mL), 0 °C, 48 h. [b] Related to benzaldehyde. [c] Isolated yield. [d] Determined by HPLC on a column with chiral stationary phase.

The temperature of 0 °C was chosen based on the results of a preliminary reaction screening. Low enantioselectivity was observed at 20 °C, and the reaction was too slow at temperatures below 0 °C. The reaction mixtures consisted merely of 2-nitroalcohol and unreacted benzaldehyde in all experiments. As can be seen from Table 1, ligand **1** or copper(II) acetate alone (Table 1, entries 1 and 2) does not catalyze the reaction. Because ligand **1** contains two binding sites for the coordination of copper(II) ions, the catalytic properties of complexes prepared at different ratios of ligand **1** to $Cu(OAc)_2 \cdot 2H_2O$ were studied (Table 1, entries 3–6). At first, concentration of the Cu(II) ions was kept constant (20 molar %) and the desired ratio was achieved by decreasing the concentration of ligand **1** (Table 1, entries 3–5). The highest yield of the product and the best enantioselectivity were achieved for a 1:1 ratio (Table 1, entry 3). When the ligand **1**: Cu(II) ratios of 1:2 or 1:10 were used (Table 1, entries 4 or 5), yield of the Henry reaction significantly dropped down but only a very small decrease in enantioselectivity was observed. If we consider that only one copper(II) ion in the dinuclear complex might be catalytically active, then actual concentration of the "catalytically active site" could decrease as we proceed from the entry 3 to entry 5 in Table 1. A lower concentration of the "catalytically active site" might lead to a lower reaction yield. Therefore, another experiment was performed, in which concentration of ligand **1** was kept constant (compared with the entry 3 in Table 1) and the desired ligand: Cu(II) ratio was achieved by increasing the concentration of Cu(II) ions (Table 1, entry 6). In that case, yield of the reaction was almost the same as in the experiment using a ligand **1**: Cu(II) ratio 1:1 and 20 molar % of both components (Table 1, entry 3). In addition, the effect of complex concentration was studied for the 1:1 ligand: copper(II) ratio (Table 1, entries 7 and 8). The results indicate that the concentration of the copper(II) complex in the reaction mixture has little effect on enantioselectivity but significantly affects yield of the Henry reaction.

To find optimal reaction conditions, three different solvents and three different copper(II) salts were tested (Table 2).

**Table 2.** Effect of counteranion and solvent on the reaction of benzaldehyde with nitromethane catalyzed by the 1:1 ligand **1**: Cu(II) complex [a].




| Entry | Cu(II) Salt | Solvent | Temperature [°C] | Reaction Time [h] | Yield [c] [%] | e.e. [d] [%] |
|---|---|---|---|---|---|---|
| 1 | $Cu(OAc)_2 \cdot 2H_2O$ | EtOH | 0 | 48 | 71 | 91 |
| 2 | $CuCl_2$ | EtOH | 0 | 48 | 38 | 93 |
| 3 [b] | $Cu(ClO_4)_2 \cdot 6H_2O$ | EtOH | 0 | - | - | - |
| 4 | $Cu(OAc)_2 \cdot 2H_2O$ | THF | 0 | 72 | 60 | 92 |
| 5 | $CuCl_2$ | THF | 0 | 72 | 0 | - |
| 6 | $CuCl_2$ | THF | 25 | 336 | 38 | 75 |
| 7 | $Cu(ClO_4)_2 \cdot 6H_2O$ | THF | 0 | 72 | 0 | - |
| 8 | $Cu(ClO_4)_2 \cdot 6H_2O$ | THF | 25 | 336 | 4 | 20 |
| 9 | $Cu(OAc)_2 \cdot 2H_2O$ | EtOAc | 0 | 48 | 14 | 90 |
| 10 | $CuCl_2$ | EtOAc | 0 | 72 | 7 | 91 |
| 11 [b] | $Cu(ClO_4)_2 \cdot 6H_2O$ | EtOAc | 0 | - | - | - |

[a] Reaction conditions: benzaldehyde (0.5 mmol), nitromethane (5 mmol), ligand **1** (0.1 mmol), Cu(II) salt (0.1 mmol), solvent (4.3 mL). [b] Insoluble complex formed. [c] Isolated yield. [d] Determined by HPLC on a column with chiral stationary phase.

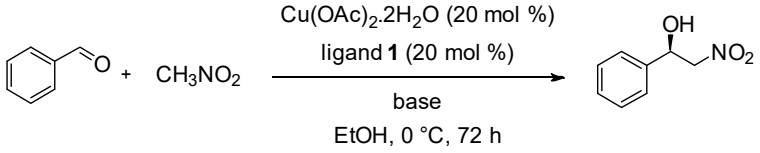
Copper(II) perchlorate formed an insoluble complex with ligand **1** in both ethanol and ethyl acetate. In such case, no product formation was observed. Copper(II) acetate proved to be the best source of the copper(II) ions, and the Henry reaction proceeded faster in ethanol then in tetrahydrofuran or ethyl acetate (Table 2, entry 1). Therefore, those two reagents were used in all subsequent experiments.

The above mentioned results confirmed that the copper(II) complex of ligand **1** catalyzes the Henry reaction of benzaldehyde with nitromethane giving (*R*)-2-nitro-1-phenylethanol in good yield and high enantioselectivity. However, the reaction is rather slow. In order to speed-up the reaction, influence of a base additive was explored. Many successful catalytic systems catalyzing the enantioselective Henry reaction contain achiral base [11,23,26,34]. Therefore, the effect of a base addition to the Cu(II) complex of ligand **1** has been studied in the reaction of benzaldehyde with nitromethane. Three bases were tested as an additive: *N*,*N*-diethylethanamine (TEA), *N*-ethyl-*N*-(propan-2-yl)propan-2-amine (DIPEA), and pyrrolidine (Table 3).

The results summarized in Table 3 suggest that addition of an achiral base led to a decrease in enantioselectivity. The best result was obtained in the experiment with 10 molar % of DIPEA added (Table 3, entry 4). In this case, the product was obtained in higher yield but enantiomeric excess decreased by 3% compared to the reaction performed in the absence of base (Table 3, entry 1). The addition of TEA or pyrrolidine did not help accelerate the reaction.

Since the best catalytic efficiency in the Henry reaction of benzaldehyde with nitromethane was observed for the catalytic system ligand **1**: $Cu(OAc)_2 \cdot 2H_2O$ (1:1) in ethanol at 0 °C, the effect of the aldehyde structure was studied under these conditions (Table 4).

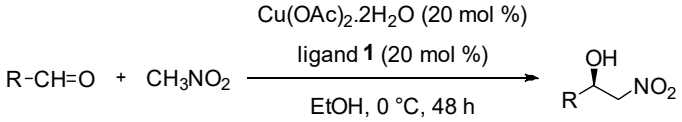
**Table 3.** Influence of a base addition on the reaction of benzaldehyde with nitromethane [a] catalyzed by the copper(II) complex of ligand **1**.




| Entry | Base | Molar Equiv. of Base [b] | Yield [c] [%] | e.e. [d] [%] |
|---|---|---|---|---|
| 1 | - | - | 74 | 88 |
| 2 | TEA | 0.1 | 75 | 83 |
| 3 | TEA | 1.0 | 66 | 78 |
| 4 | DIPEA | 0.1 | 83 | 85 |
| 5 | DIPEA | 1.0 | 89 | 60 |
| 6 | pyrrolidine | 0.1 | 45 | 83 |
| 7 | pyrrolidine | 1.0 | 36 | 74 |

[a] Reaction conditions: benzaldehyde (0.2 mmol), nitromethane (2 mmol), ligand **1** (0.04 mmol), copper(II) acetate (0.04 mmol), ethanol (2.0 mL), 0 °C, 72 h. [b] Related to benzaldehyde. [c] Isolated yield. [d] Determined by HPLC on a column with chiral stationary phase.

**Table 4.** Effect of the aldehyde structure on yield and enantioselectivity of the Henry reaction [a].



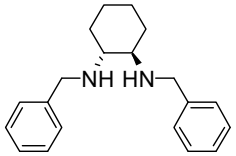

| Entry | Aldehyde | Yield [b] [%] | e.e. [c] [%] |
|---|---|---|---|
| 1 | 4-bromobenzaldehyde | 82 | 75 |
| 2 | 4-methylbenzaldehyde | 68 | 85 |
| 3 | 4-nitrobenzaldehyde | 50 | 85 |
| 4 | 2-methylpropanal | 18 | 85 |
| 5 | hexanal | 12 | 85 |
| 6 | cyclohexanecarbaldehyde | 21 | 83 |
| 7 | 3-phenylpropanal | 25 | 88 |

[a] Reaction conditions: aldehyde (0.2 mmol), nitromethane (2 mmol), ligand **1** (0.04 mmol), copper(II) acetate (0.04 mmol), ethanol (2.0 mL), 0 °C, 48 h. [b] Isolated yield. [c] Determined by HPLC on a column with chiral stationary phase.

The results of this study indicate that both aromatic and aliphatic aldehydes gave relatively good enantioselectivities. However, yield of the Henry reaction was significantly lower when the starting aldehyde was the aliphatic one. Among all studied aldehydes, 4-bromobenzaldehyde exhibited the highest yield but the lowest enantioselectivity. The presence of an electron-donating group in the *para*-position of the aromatic aldehyde appears to have a positive effect on the reaction yield.

## 3. Discussion

The present study of the catalytic properties of the copper(II) complexes of bis(*trans*-cyclohexane-1,2-diamine)-based ligand **1** answered a question of whether the second copper (II) ion in the dinuclear copper(II) complex might somehow contribute to catalysis of the enantioselective Henry reaction. A comparison of our preliminary results with the catalytic properties of the copper(II) complexes of (1*R*,2*R*)-*N*,*N*′-dibenzylcyclohexane-1,2-diamine (**6**, Figure 2) published in the literature [22,23] raised expectations that second copper(II) ion might participate in the catalytic process.




**6**

**Figure 2.** Structure of ligand **6**.

Diamine **6** is structurally similar to ligand **1** but possess only one enantiomerically pure cyclohexane-1,2-diamine unit. In 2007, Bandini et al. [22] reported only 56% conversion and 51% e.e. in the reaction of benzaldehyde with nitromethane catalyzed by 12% of the $Cu(OAc)_2$-**6** catalyst. The reaction was carried out in ethanol at room temperature for 1.2 h. Later, Jeong et al. [23] published the same reaction catalyzed by 10% of the $CuCl_2$-**6** complex with the addition of 6% of achiral base. They run the reaction in methanol at room temperature for one week using TEA as an additional base and isolated (*S*)-2-nitro-1-phenylethanol in 53% yield and 39% e.e. Significantly higher enantioselectivities (in the range of 85–90% e.e.) were observed in our preliminary experiments, in which we catalyzed the same reaction with the $Cu(OAc)_2$-**1** complex.

However, our further studies (Table 1) revealed that the best results were obtained for the ligand **1**: copper(II) acetate ratio = 1:1, where the mononuclear complex is the main catalytic species. This observation contradicted the presumed idea of cooperation between the two metal centers in the course of the Henry reaction. To obtain directly comparable data, we repeated the Henry reaction of benzaldehyde with nitromethane catalyzed by the $Cu(OAc)_2$-**6** complex under the same reaction conditions as optimized for ligand **1**. The catalyst was formed in situ by mixing $Cu(OAc)_2 \cdot 2H_2O$ and ligand **6** in the 1:1 ratio. The reaction was carried out in ethanol at 0 °C for 72 h using 20 molar % of catalyst without any additional base. After work-up, (*S*)-2-nitro-1-phenylethanol was isolated in 64% yield and 89% e.e., i.e., in distinctly higher e.e. than was previously reported [22,23]. Supposedly, higher catalyst loading and lower temperature are responsible for this improvement in e.e. The reaction catalyzed by the $Cu(OAc)_2$-**6** complex proceeded more slowly than that of catalyzed by the $Cu(OAc)_2$-**1** complex, and yield of the product was slightly lower as well. However, the enantioselectivities achieved were almost the same for both catalysts. This observation complemented our previous results and led us to conclude that only one copper(II) ion is engaged in catalysis of the Henry reaction. The faster reaction rate of the Henry reaction catalyzed by the $Cu(OAc)_2$-**1** (1:1) complex compared to the reaction catalyzed by the $Cu(OAc)_2$-**6** complex might be explained by the presence of basic secondary amino groups in the close proximity of the catalytic center.

In conclusion, we demonstrated that the $Cu(OAc)_2$-**1** (1:1) complex catalyzes the enantioselective Henry reaction of various aldehydes with nitromethane. To achieve good enantioselectivities, relatively high catalyst loading (20 molar %) and low temperatures are necessary. The best results were obtained in the Henry reaction of aromatic aldehydes using copper(II) acetate as a copper(II) salt and ethanol as a solvent in the absence of achiral base.

## 4. Materials and Methods

### *4.1. General Methods*

Melting points were determined on an Electrothermal IA 9100 melting point apparatus. Elemental analyses were done in the Analytical Laboratory of the Institute of Organic Chemistry and Biochemistry AS CR using a Perkin Elmer 2400 II instrument (Waltham, MA, USA). Optical rotations were recorded on a Perkin-Elmer 241 polarimeter; specific optical rotations [$\alpha$] and concentrations c are given in $deg \cdot 10^{-1} \cdot m^2 \cdot g^{-1}$ and g/100 mL, respectively. FTIR spectra were measured on a Nicolet 6700 instrument (Thermo Scientific, Waltham, MA, USA). NMR spectra were recorded on a Varian (Palo Alto, CA, USA) Mercury Plus spectrometer ($^1$H NMR at 299.97 MHz; $^{13}$C NMR at 75.43 MHz) and on

an Agilent (Santa Clara, CA, USA) MR DDR2 spectrometer ($^1$H NMR at 399.94 MHz; $^{13}$C NMR at 100.58 MHz). All NMR measurements were carried out at rt. Chemical shifts δ are reported in ppm and are referenced to the signals of residual non-deuterated solvents ($CDCl_3$ $\delta_H$ 7.26, $\delta_C$ 77.16; DMSO-$d_6$ $\delta_H$ 2.50, $\delta_C$ 39.50). Coupling constants *J* are given in Hz. Mass spectra were measured on a Waters (Milford, MA, USA) Micromass ZQ (low resolution) or a Thermo Scientific (Waltham, MA, USA) LTQ Orbitrap Velos (high resolution) spectrometer with electrospray ionization. TLC analyses were carried out on aluminum foils coated with Silica gel 60 $F_{254}$ (Merck, Darmstadt, Germany) and compounds were detected under UV light (λ = 254 nm) or visualized by a treatment with 3% aqueous $KMnO_4$ and heating. Silica gel (Fluka, 63–200 μm) was used for preparative column chromatography. HPLC analyses were done on an Ecom (Prague, Czech Republic) instrument (pump LCP4100, UV detector LCD2083, software CSW32) using the Supelcosil LC-Si (250 × 4.6 mm; 5 μm), YMC Chiral ART Amylose-SA (250 × 4.6 mm; 5 μm) and YMC Chiral Cellulose-SB (250 × 4.6 mm; 5 μm) columns. Dry ethanol was obtained from a PureSOLV PS-MD-7 (VWE International) drying column. Benzaldehyde was successively washed with 10% aqueous $Na_2CO_3$, saturated aqueous $Na_2SO_3$, and water, and then was dried over $MgSO_4$. Upon the drying agent removal, benzaldehyde was distilled under reduced pressure. Nitromethane was distilled and kept under 5 °C prior to use. Compound **2** was prepared according to literature procedure [33]. Other chemicals and solvents were used as received from commercial sources (Sigma-Aldrich, Darmstadt, Germany; Fluorochem, Hadfield, UK; Penta s.r.o., Prague, Czech Republic). Syntheses of racemic standards of 2-nitroalcohols can be found in the Supplementary Materials.

### *4.2. Di-tert-butyl [(1S,1′S,2S,2′S)-{[1,4-phenylenebis(methaneylylidene)]bis(azaneylylidene)} bis(cyclohexane-2,1-diyl)]dicarbamate* (**3**)

A solution of terephthaldehyde (1.09 g, 8.1 mmol) in acetonitrile (30 mL) was added to a solution of carbamate **2** (3.48 g, 16.2 mmol) in acetonitrile (100 mL). The reaction mixture was stirred at rt for 18 h. The white precipitate was isolated by filtration and washed with cold acetonitrile (50 mL). The precipitate was re-crystallized from ethyl acetate giving product **3** (3.45 g, 6.5 mmol, 80%) as a white solid; M.p. 238–239 °C; Anal. for $C_{30}H_{46}N_4O_4$ calcd. (%) C 68.41, H 8.80, N 10.64; found (%) C 67.9, H 8.6, N 10.3; $[\alpha]_D^{20}$ +94.2 (*c* 0.4, $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$): δ 8.26 (2H, s, CH=N), 7.75 (4H, s, ArH), 4.26 (2H, br s, CONH), 3.76–3.50 (2H, m, CHN), 3.13–2.89 (2H, m, CHN), 2.21–1.98 (2H, m, $CH_2$), 1.93–1.64 (8H, m, $CH_2$), 1.53–1.13 (6H, m, $CH_2$), 1.27 (18H, s, $CH_3$); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 159.7, 155.2, 138.1, 128.4, 79.0, 74.8, 54.2, 33.3, 32.0, 28.3, 25.0, 24.2; MS (ESI) *m*/*z* 549 ($[M + Na]^+$).

### *4.3. Di-tert-butyl [(1S,1′S,2S,2′S)-{[1,4-phenylenebis(methylene)]bis(azanediyl)}bis(cyclohexane-2, 1-diyl)]dicarbamate* (**4**)

Sodium borohydride (0.88 g, 23.0 mmol) was added to a solution of diimine **5** (3.23 g, 6.1 mmol) in a methanol/tetrahydrofuran mixture (125 mL/125 mL). The reaction mixture was stirred at rt for 18 h. Water (100 mL) was added and the product was extracted into dichloromethane (3 × 100 mL). The combined organic phases were dried over $Na_2SO_4$, filtered, and the solvent was evaporated in vacuo. The crude product was crystallized from a dichloromethane/acetonitrile (1:1) mixture at 5 °C. The white crystals were isolated and dried in vacuo to afford dicarbamate **4** (3.07 g, 5.8 mmol, 95%); M.p. 180–181 °C; Anal. for $C_{30}H_{50}N_4O_4$ calcd. (%) C 67.89, H 9.50, N 10.56, found (%) C 67.5, H 9.4, N 10.4; $[\alpha]_D^{20}$ +28.6 (*c* 1.0, $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$): δ 7.26 (4H, s, ArH), 4.47 (2H, br s, CONH), 3.88 (2H, d, *J* 13.2 Hz, $ArCH_aH_bN$), 3.66 (2H, d, *J* 13.2 Hz, $ArCH_aH_bN$), 3.44–3.22 (2H, m, CHN), 2.34–2.22 (2H, m, CHN), 2.17–1.96 (4H, m, $CH_2$), 1.78–1.59 (6H, m, $CH_2$ + $CH_2NHCH$), 1.45 (18H, s, $CH_3$), 1.34–0.96 (8H, m, $CH_2$); $^{13}$C NMR (101 MHz, $CDCl_3$): 156.0, 139.5, 128.1, 79.1, 60.4, 54.2, 50.2, 32.9, 31.6, 28.4, 24.9, 24.6; MS (ESI) *m*/*z* 532 ($[M + H]^+$). NMR spectra are in accordance with those previously published [32].

### *4.4. (1S,1′S,2S,2′S)-N1,N1′-[1,4-Phenylenebis(methylene)]bis(cyclohexane-1,2-diamine)* (**5**)

Trifluoroacetic acid (20 mL) was added to a solution of dicarbamate **6** (800 mg, 1.5 mmol) in dichloromethane (20 mL) and the mixture was stirred at rt for 3 h. The solvents were evaporated in vacuo and the obtained oil was vigorously stirred with a saturated aqueous solution of KOH (10 mL) for 10 min. The mixture was extracted with ethyl acetate (3 × 60 mL). The combined organic layers were dried over $Na_2SO_4$, filtered, and the solvent was evaporated in vacuo to give tetraamine **5** (486 mg, 1.5 mmol, 98%) as yellow oil; $^1$H NMR (300 MHz, DMSO-$d_6$): δ 7.24 (4H, s, ArH), 3.77 (2H, d, *J* 13.3 Hz, $ArCH_aH_bN$), 3.55 (2H, d, *J* 13.3 Hz, $ArCH_aH_bN$), 2.28–2.15 (2H, m, CHN), 2.03–1.84 (4H, m, CHN + $CH_2$), 1.79–1.67 (2H, m, $CH_2$), 1.62–1.56 (4H, m, $CH_2$), 1.22–0.83 (8H, m, $CH_2$); $^{13}$C NMR (101 MHz, DMSO-$d_6$): δ 140.1, 128.1, 62.8, 55.1, 50.4, 35.4, 31.0, 25.3, 25.2; MS (ESI) *m*/*z* 331 ($[M + H]^+$).

### *4.5. (1S,1′S,2S,2′S)-$N^1$,$N^{1'}$-[(1,4-Phenylenebis(methylene)]bis($N^2$-benzylcyclohexane-1, 2-diamine)* (**1**)

Benzaldehyde (382 mg, 0.37 mL, 3.60 mmol) was added to a solution of tetramine **5** (540 mg, 1.64 mmol) in acetonitrile (20 mL) and the reaction mixture was stirred at rt for 18 h. The solvent was evaporated in vacuo and the residue (crude diimine) was dissolved in a methanol/tetrahydrofuran (20 mL/20 mL) mixture. Sodium borohydride (244 mg, 6.46 mmol) was added and the reaction mixture was stirred at rt for 18 h. Water (20 mL) was added and product was extracted into dichloromethane (3 × 60 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated in vacuo. The crude product was obtained as orange oil (800 mg). It was dissolved in water (20 mL) and pH of the solution was adjusted to 6 using conc. HCl while vigorously stirring. The mixture was stirred at rt for additional 20 min, then a solution of $NH_4PF_6$ (1.46 g, 8.9 mmol) in water (5 mL) was added and the mixture was cooled to 5 °C for 18 h. The white precipitate was isolated and dissolved in a vigorously stirred biphasic mixture of dichloromethane (20 mL) and saturated aqueous solution of NaOH (20 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated in vacuo to give ligand **1** as yellowish oil (491 mg, 0.97 mmol, 59%); $[\alpha]_D^{20}$ +87.7 (*c* 0.3, $CHCl_3$); IR $\nu_{max}$ (liquid film): 3297, 3025, 2926, 2854, 1453, 1275, 1260, 1116 $cm^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 7.30–7.10 (14H, m, ArH), 3.75 (4H, dd, *J* 13.3, 6.3 Hz, $ArCH_2N$), 3.55 (4H, dd, *J* 13.3, 7.4 Hz, $ArCH_2N$), 2.22–2.09 (4H, m, CHN), 2.06–1.92 (4H, m, $CH_2$), 1.68–1.53 (4H, m, $CH_2$), 1.20–1.06 (4H, m, $CH_2$), 1.05–0.80 (4H, m, $CH_2$); $^{13}$C NMR (101 MHz, DMSO-$d_6$): δ 141.8, 139.9, 128.5, 128.3, 128.1, 126.9, 67.5, 60.6, 50.3, 50.1, 31.1, 31.0, 25.6, 25.0; HRMS (ESI) for $C_{34}H_{46}N_4$ ($[M + H]^+$) calcd. 511.3795, found 511.3792.

### *4.6. Typical Procedure for the Henry Reaction*

Ligand **1** (51 mg, 0.1 mmol) and $Cu(OAc)_2{\cdot}2H_2O$ (22 mg, 0.1 mmol) were dissolved in dry ethanol (4.0 mL) and the solution was stirred at rt for 15 min. The mixture was cooled to 0 °C and benzaldehyde (53 mg, 51 μL, 0.5 mmol) was added, followed by addition of nitromethane (122 mg, 107 μL, 2 mmol). The reaction mixture was stirred at 0 °C for 48 h and then concentrated in vacuo. The residue was subjected to a column chromatography in a hexane/ethyl acetate (4:1) mixture. 2-Nitro-1-phenylethan-1-ol was obtained as a light yellow oil (59 mg, 0.35 mmol, 71%); TLC $R_f$ (hexane/ethyl acetate 85:15) 0.2; $^1$H NMR (300 MHz, $CDCl_3$): δ 7.53–7.30 (5H, m, ArH), 5.48 (1H, dd, *J* 9.4, 3.2 Hz, CH), 4.68–4.45 (2H, m, $CH_2$), 2.83 (1H, br s, OH); $^{13}$C NMR (400 MHz, $CDCl_3$) δ 138.3, 129.1, 129.0, 126.1, 81.3, 71.1. The analytical data are in accordance with those published previously [35]. Enantiomeric excess was determined by means of HPLC analysis on the YMC Chiral Cellulose-SB column (250 × 4.6 mm; 5 μm) using a heptane/propan-2-ol (9:1) mixture at flow rate of 1 mL/min with UV detection at 210 nm. The individual peaks were assigned to particular enantiomers by comparison with HPLC analyses done on a column with

chemically equivalent chiral stationary phase [35]: $t_{(R)}$ = 15.1 min (major), $t_{(S)}$ = 17.7 min (minor); e.e. 91%.

**Supplementary Materials:** The following are available online at https://www.mdpi.com/2073-4344/11/1/41/s1. Syntheses of compounds **2**, **6** and racemic 2-nitroalcohols, copies of $^{1}$H NMR, $^{13}$C NMR and MS spectra and HPLC chromatograms.

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