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Asymmetric Henry reaction catalyzed by chiral secondary diamine-copper(II) complexes

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ABSTRACT

The enantioselective Henry reaction was efficiently carried out under mild reaction conditions in 96% ethanol. The chiral C_2-symmetric, secondary bisamines based on the 1,2-diaminocyclohexane framework and copper(II) acetate were found to promote the asymmetric nitroaldol reaction. Aromatic and aliphatic aldehydes were reacted with nitromethane to provide the corresponding β-nitroalcohols in very good yields and enantioselectivities up to 94%.

1. Introduction

The asymmetric Henry (nitroaldol) reaction provides easy access to chiral β-nitroalcohols. These products can be further converted into valuable chiral building blocks, such as 1,2-aminoalcohols, α-hydroxy acids, 1,2-diamines, and other precursors of biologically active compounds.[1] Due to the practical importance of the reaction, much attention has been paid to its enantioselective derivatives. Both organocatalytic and metal-catalyzed protocols have been developed so far.[2] Chiral copper complexes have, in particular, attracted much interest in this respect, and in some cases afforded nitroaldols with impressive enantioselectivities.[3] Both secondary[3h,i,n] and tertiary amines[3c,j] are amongst the successfully applied ligands, providing β-nitroalcohols with ee's up to 99%. Despite significant advances in this field, there are some shortcomings such as rather complex ligand structures, substrate specificity limitations or the need for anhydrous reaction conditions. All these obstruct the general use of the direct nitroaldol reaction, and encourage further research.

Chiral secondary vic-diamines can be synthesized in a simple way from the readily available precursors.[4] They have turned out to be effective ligands for many metal-catalyzed asymmetric transformations.[3h,l,n,5b,7] In spite of the increased acidity of the N–H proton,[6] they form stable metal complexes creating a chiral environment for the catalytic reaction. The stereogenic centers are located in the carbon skeleton, and after complexation at the nitrogen atoms as well.[7] The potential merits of this chiral framework along with the recent results obtained by Bandini et al. for ligands of this type with thienyl pedants[3h] encouraged us to evaluate more broadly simple C_2-symmetric secondary diamines in the asymmetric nitroaldol reaction.

2. Results and discussion

Thus, in order to correlate their catalytic activity and selectivity, we obtained a set of ligands with heteroaromatic, *ortho*-, *meta*- and *para*-substituted as well as with branched, aromatic moieties. Various chiral diamines were prepared by a two-step synthesis starting from easily available (1*R*,2*R*)-(+)-1,2-diaminocyclohexane L-tartrate and the respective aldehydes with no need for purification of the imine[4] (Scheme 1). The corresponding tertiary diamine **1o** was obtained from **1n** via its N-methylation according to the literature procedure.[8]

Next, ligands **1a**–**o** were examined in the reaction of nitromethane with benzaldehyde in the presence of 12 mol % of chiral diamine and 10 mol % of $Cu(OAc)_2$. We found that unlike in Bandini's[3h] protocol, moisture and air do not have to be avoided in this reaction (see below). Thus, water containing ethanol (96%) was generally used as a solvent under aerobic conditions at 0 °C.[9] The results summarized in Table 1 show that these conditions simultaneously gave good yield and enantiomeric excess for the desired product (see Scheme 2).

The ligands with *ortho*-substituted aromatic moieties **1f**–**i**, **m**, and a 2,6-disubstituted one **1l** gave products with up to 84% ee. Among them, those with 2-chloro **1i** and 2,6-dichloro **1l** substituents afforded relatively better results, while the presence of electron-donating groups in **1f** and **1h** gave ee of only 66% and 67%, respectively. Increasing the steric hindrance in **1g** further did not improve enantioselectivity.

The best results were obtained for ligands **1a**, **1b**, **1j**, **1k**, and **1n** with ee's close to each other, regardless of the differences in size and electronic character of their aromatic moieties. It is notable that tertiary diamine **1o**, in comparison to **1n**, gave lower yields and enantioselectivities.

Further experiments (Table 2) were carried out using **1k**. Thus, under Bandini's reaction conditions (23 °C in absolute ethanol)[3h]

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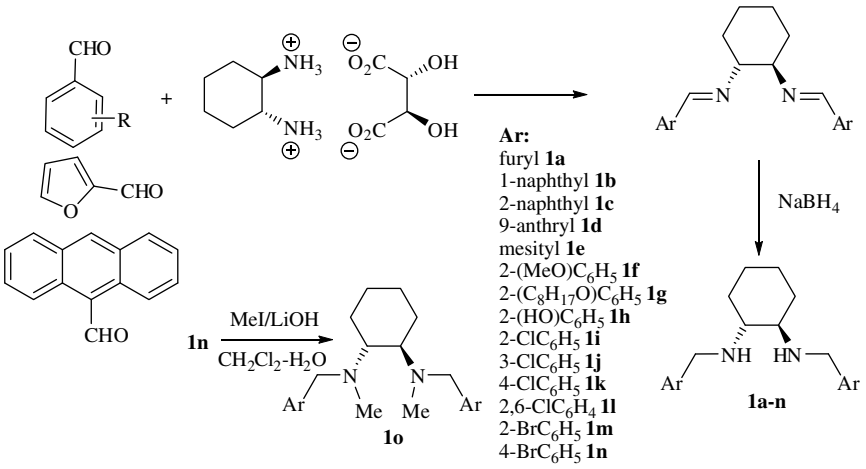
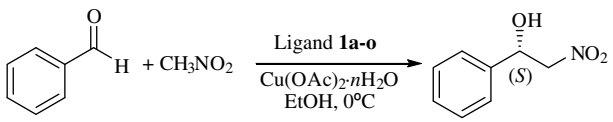


Scheme 1.

Table 1
Screening diamine ligands in the Henry reaction of benzaldehyde and nitromethane[a]

Entry	Ligand[b]	Yield[c] (%)	ee[d] (%)
1[e]	**1a**	62	87
2[e,f]	**1a**	57	89
3[e,g,f]	**1a**	43	56
4[g,f]	**1a**	59	63
5	**1a**	80	89
6[f]	**1a**	75	91
7	**1b**	92	81
8	**1c**	47	86
9	**1d**	82	90
10[h]	**1d**	79	87
11	**1e**	94	53
12	**1f**	83	67
13	**1g**	92	68
13	**1h**	19	66
14	**1i**	79	82
15	**1j**	86	89
16	**1k**	95	91
17	**1l**	69	84
18	**1m**	82	78
19	**1n**	99	89
20	**1o**	42	77

[a] Reactions were performed on a 0.5 mmol scale, 12 mol % of respective diamine **1a**–**1o**, 10 mol % of $Cu(OAc)_2{\cdot}nH_2O$, 10 equiv of CH_3NO_2 in ethanol (96%) at 0 °C for 48 h.
[b] Ligand structure according to Scheme 1.
[c] Yield of isolated product.
[d] Enantiomeric excess determined by HPLC using Chiracel OD-H column.
[e] Evaporation under reduced pressure before purification of the product by chromatography.
[f] Reaction was performed in 2-propanol.
[g] Reaction was performed at 23 °C.
[h] Reaction was performed in nitromethane.



Scheme 2.

with this ligand, the product was obtained with 91% ee and 89% conversion (^{1}H NMR) after 80 min. The reaction performed under these conditions for 16 h resulted in 95% yield and 85% ee (entry 2). The same enantioselectivity was observed for reaction in 96% ethanol (entry 3) after 16 h. Decreasing the reaction temperature to 0 °C caused the stereoselectivity to increase to 90% ee, although with significant lowering of the yield after 16 h (entry 4). Running this experiment for 48 h, 95% yield and 91% ee were obtained (entry 6). After changing the molar ratio of ligand/copper from 1.2 to 2.4, the yield decreased to 42% without any changes in ee (entry 5). Halving the amounts of both the ligand and copper salt caused no change in the stereoselectivity (90%), but the yield was lowered slightly (entry 7). Interestingly, in the presence of **1k**, but without a Cu-salt no nitroalcohol product was detected (unreacted aldehyde was recovered in 94%). This implies that the ligand itself, as an amine, is not a suitable promoter for this reaction.[10]

Table 2
Nitroaldol reaction of benzaldehyde and nitromethane catalyzed by **1k**–$Cu(OAc)_2$[a]

Entry	T (°C)	Yield[b] (%)	ee[c] (%)
1[d,e]	23	89 (NMR)	91
2[d]	23	95	85
3	23	75	85
4	0	32	90
5	0	42	93
6	0	95	91
7[f]	0	81	90
8[g]	0	48	91
9[g,h]	0	99	80
10[g,i]	0	77	92

[a] Reactions were performed on a 0.5 mmol scale, 12 mol % of diamine **1k**, 10 mol % of $Cu(OAc)_2{\cdot}nH_2O$, 10 equiv of CH_3NO_2 in ethanol (96%) for 48 h.
[b] Yield of isolated product.
[c] Enantiomeric excess determined by HPLC on a Chiracel OD-H column.
[d] Bandini's protocol was applied: dry EtOH, dried glassware under argon.
[e] Conversion by ^{1}H NMR after 80 min.
[f] 6 mol % of **1k** and 5 mol % of $Cu(OAc)_2{\cdot}nH_2O$ was used.
[g] Complex **2** was used.
[h] 10 mol % of DIPEA was used.
[i] 2 mol % of DIPEA was used.

To learn more about the nature of the catalyst, complex **1k**–$Cu(OAc)_2$ **2** was prepared and isolated in 61% yield upon single crystallization from CH_2Cl_2/*n*-hexane. Its application to the nitroaldol reaction revealed that the desired product was obtained in 91% ee and 48% yield after 48 h at 0 °C (Table 2, entry 8). The yield of the product increased up to 99% when 10 mol % of DIPEA was added with some loss of ee (entry 9). When the reaction was performed with only 2 mol % of DIPEA, the nitroalcohol was obtained in 92% ee and 77% yield (entry 10).

The reaction catalyzed by (*R*,*R*)-**1a**–**o** copper complexes, as well as by the Bandini[3h] system, led to the corresponding β-nitroalcohol with an (*S*)-configuration at the stereogenic center. Having in mind

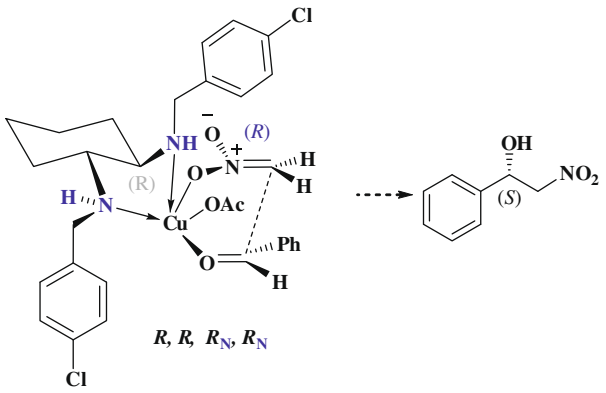


Figure 1. Transition state model explaining the observed stereochemical outcome.

both possible complexes with the different absolute configurations at the nitrogen atoms,[7] a plausible mechanism can be represented by the transition state model shown in Figure 1.

According to the previously reported considerations,[3a,b] we assume the coordination mode where the carbonyl oxygen atom is coordinated at one of the equatorial positions, and the oxygen atom of nitromethane approaches the metal center from the axial side. This positioning of the reactants seems the most favorable orientation taking into account steric and electronic considerations, and ensures activation of both electrophile and nucleophile. Thus, after deprotonation by an acetate anion[3b] or by the other external base, the resulting nitronate ion approaches the aldehyde from the *Re* face (Fig. 1) to give the observed (*S*)-product. Other possibilities seem to be restricted by the unfavorable steric interactions between the phenyl group of the aldehyde and aromatic moiety of the ligand.

Based on this reasoning and the X-ray structure of Bandini's complex,[3h] we can assume that stereoselectivity in this reaction results from the configuration on the nitrogen and distribution of the possible diastereomeric complexes. The conformation of the resulting diamine-copper species (R,R,R_N,R_N), where the largest substituents on nitrogen are parallel to each other and oriented in opposite directions, is then similar to those observed for effective copper–BOX complexes.[3a,b]

Table 3
Nitroaldol reaction of aldehydes (RCHO) and nitromethane catalyzed by **1k**–$Cu(OAc)_2$[a]

Entry	R	Yield[b] (%)	ee[c] (%)
1	Ph	95	91
2	*p*-PhC_6H_4	87	83
3[d]	*p*-PhC_6H_4	91	83
4[e]	*p*-PhC_6H_4	83	89
5	*p*-ClC_6H_4	94	83
6	*p*-$O_2NC_6H_4$	99	82
7	*p*-MeC_6H_4	76	81
8	2-Naphthyl	89	80
9	1-Naphthyl	91	86
10	*o*-$MeOC_6H_4$	79	83
11	*m*-ClC_6H_4	90	87
12	PhCH=CH–	77	94
13	*c*-C_6H_{12}	65	85
14	2-Furyl	64	79
15	*t*-Bu	67	92

[a] Reactions were performed on a 0.5 mmol scale, 12 mol % of ligand **1k**, 10 mol % of $Cu(OAc)_2 \cdot nH_2O$, 10 equiv of CH_3NO_2 in ethanol (96%) at 0 °C for 48 h.
[b] Yield of isolated product.
[c] Enantiomeric excess determined by HPLC on Chiracel OD-H or Chiralpak AD-H columns.
[d] Ligand **1d** was applied.
[e] Ligand **1a** was applied.

In order to examine the scope of the reaction, we applied ligand **1k** (12 mol %) hydrated $Cu(OAc)_2$ (10 mol %) in EtOH (96%) to the nitroaldol reaction of various aldehydes (Table 3).

A variety of 2, 3 or 4-substituted aromatic, heteroaromatic, and aliphatic aldehydes provided respective β-nitroalcohols with good to high yields (up to 99%) and with enantioselectivities ranging from 79% to 94%. It should be noted that the electronic character of the substituent as well as its steric hindrance has rather slight influence on the enantioselectivities. The ligands which were effective in the nitroaldol reaction of benzaldehyde **1a**, **1d**, and **1k** performed equally well with a branched substrate namely *p*-biphenylcarbaldehyde (entries 2–4). Aldehydes with electron-withdrawing substituents led to products with higher yields, and this result correlates with the increased electrophilicity of the substrate.

Encouraged by the efficiency of the **1k**–$Cu(OAc)_2$ catalytic system, we also performed the reaction between benzaldehyde and nitroethane. Unfortunately, the corresponding diastereoisomeric products were obtained in low ee (major 27%, minor 30%) and poor total yield (19%).

3. Conclusion

In conclusion, we have presented the application of simple chiral secondary diamines obtained from 1,2-diaminocyclohexane to the asymmetric nitroaldol reaction. The product formation required 12 mol % of ligand and 10 mol % of $Cu(OAc)_2$ hydrate under mild conditions in 96% aq ethanol. Commercial grade solvent and reagents were applied without any precautions to provide products with good to excellent yields and enantioselectivities up to 94%. The reaction stereochemical outcome was in agreement with the generally accepted transition state model.

4. Experimental

4.1. General

^1H NMR and ^{13}C NMR spectra were measured on a Bruker Avance DRX (^1H, 300 MHz) spectrometer using TMS as an internal standard. Observed rotations at 589 nm were measured using an Optical Activity Ltd. Model AA-5 automatic polarimeter. High-resolution mass spectra (HRMS) were recorded on a Mariner PE Biosystems unit using the ESI technique. The enantiomeric composition of nitroaldols was determined by HPLC analysis using a chiral stationary phase (Chiracel OD-H or Daicel Chiralpak AD-H). The absolute configuration of the major enantiomer was assigned according to the sign of the specific rotation as well as of the retention time with the reported data.[3b,i]

Separations of products by chromatography were performed on Silica Gel 60 (230–400 mesh) purchased from Fluka. Thin layer chromatography analyses were performed using Silica Gel 60 percolated plates (Fluka). Ethanol was dried by heating with CaH_2 followed by distillation prior to use. For the general applications, ethanol 96% (aq) was used without any precautions. Liquid aldehydes were freshly distilled before use.

4.2. Ligands

Diamines **1a**,[7b] **1b**,[7b,11] **1d**,[12] **1e**,[11,13] **1f**,[14] **1h**,[15] and **1n**[12] are known compounds. For other ligands, procedures are presented below.

4.2.1. General procedure[4b] for ligands 1c, 1i, 1j, 1k, 1m

Potassium bicarbonate (anhydrous, 2.0 equiv) was added to vigorously stirred suspension of (1*R*,2*R*)-(+)-1,2-diaminocyclohexane

L-tartrate salt (1.0 equiv) in water (46 mL/10 mmol of salt) at rt. Then ethanol (96%, 20 mL/10 mmol of salt) was added, followed by solution of an aldehyde (2.0 equiv) and CH_3SO_3H (0.1 mL) in dichloromethane. The biphasic mixture was stirred at rt overnight, refluxed for 2 h, and concentrated in vacuo to evaporate organic solvents. After cooling, ethyl acetate was added (50 mL), the phases were separated, and the water layer was washed with AcOEt (3×50 mL). Combined organic layers were dried over Na_2SO_4 and solvent was evaporated in vacuo giving a crude diimine, which was directly used in the next step.

The diimine was dissolved in MeOH (5 mL/10 mmol). In the case of non-soluble compounds, toluene was added to dissolution. The resulting mixture was cooled on an ice-bath, and $NaBH_4$ (2.5 equiv) was added in one portion. Stirring at this temperature was maintained until gas evaporation was stopped, and then the mixture was allowed to reach rt and then refluxed for 2 h. The solvents were removed in vacuo and the residue was treated with water (50 mL/10 mmol of salt) and dichloromethane (50 mL/10 mmol of salt). Phases were separated, and the upper layer was washed with CH_2Cl_2. The combined organic fractions were dried over K_2CO_3, and the solvent was evaporated in vacuo. The product was purified by column chromatography on silica gel (50 g/10 mmol of salt, gradient $CHCl_3$ to $CHCl_3$/MeOH, 10:1, v/v) giving the desired product.

4.2.2. Compound 1c

Ligand **1c** was prepared according to the general procedure starting from (1*R*,2*R*)-(+)-1,2-diaminocyclohexane L-tartrate salt (500 mg, 1.9 mmol). The crude imine (628 mg) was reduced to afford 399 mg (54% yield after two stages) of the desired product as a light yellow solid, mp = 74–76 °C; $R_f = 0.31$ ($CHCl_3$/EtOH, 20:1, v/v), $[\alpha]_D = +15.9$ (*c* 0.4, MeOH); IR (film): ν_{max} 3297, 3051, 2925, 2856, 1599, 1508, 1450, 1126, 855, 813, 744, 473 cm^{-1}; ^1H NMR δ 7.74–7.83 (m, 8H, ArH), 7.41–7.49 (m, 6H, ArH), 4.08 (d, $J = 13.2$ Hz, 2H, CH_AH_B), 3.83 (d, $J = 13.2$ Hz, 2H, CH_AH_B), 2.32–2.35 (m, 2H, $2 \times CHN$), 2.21 (br d, $J = 11.4$ Hz, 2H, CH_2), 2.02 (s, 2H, $2 \times NH$), 1.73–1.76 (m, 2H, CH_2), 1.22–1.28 (m, 2H, CH_2), 1.06–1.09 (m, 2H, CH_2). ^{13}C NMR δ 139.0 (C_{Ar} IV°), 133.8 (C_{Ar} IV°), 132.9 (C_{Ar} IV°), 128.2 (C_{Ar}), 128.0 (C_{Ar}), 127.9 (C_{Ar}), 127.0 (C_{Ar}), 126.5 (C_{Ar}), 126.2(C_{Ar}), 125.7 (C_{Ar}), 61.2 (CHN), 51.2 (CH_AH_B), 31.9 (CH_2), 25.4 (CH_2). HRMS (ESI, $[M+H]^+$) calcd for $[C_{28}H_{30}N_2+H]^+$ 395.2482; found 395.2466.

4.2.3. Compound 1g

(1*R*,2*R*)-Diaminocyclohexane (71 mg, 0.62 mmol, 1.0 equiv) in toluene (2.0 mL) was added to the solution of the aldehyde (293 mg, 1.25 mmol, 2.0 equiv) in toluene (4.0 mL), followed by anhydrous $MgSO_4$ (3.0 g). The resulting solution was stirred vigorously for 24 h at rt, heated at reflux for 1 h, and then cooled. The solid was filtered, and washed with toluene (2×10 mL). The filtrate was concentrated in vacuo, dried under high vacuum giving 320 mg of crude oily imine. The reduction was performed following the general procedure affording 190 mg (55% yield after two stages) of a colorless oil; $R_f = 0.72$ ($CHCl_3$/EtOH, 20:1, v/v), $[\alpha]_D = -33.0$ (*c* 0.2, MeOH); IR (film): ν_{max} 3312, 2927, 2855, 1601, 1493, 1455, 1242, 1106, 751 cm^{-1}; ^1H NMR δ 7.22 (dd, $J = 7.2$, 1.5 Hz, 2H, ArH), 7.16 (dt, $J = 7.9$, 1.5 Hz, 2H, ArH), 6.85 (t, $J = 7.2$ Hz, 2H, ArH), 6.77 (d, $J = 7.9$ Hz, 2H, ArH), 3.83–3.93 (m, 6H, $2 \times CH_2O + CH_AH_B$), 3.61 (d, $J = 13.2$ Hz, 2H, CH_AH_B), 2.50 (br s, 2H, $2 \times NH$), 2.21–2.24 (m, 2H, $2 \times CHN$), 2.13 (br d, $J = 12.6$ Hz, 2H, CH_2), 1.65–1.70 (m, 6H, $3 \times CH_2$), 1.18–1.37 (m, 22H, $11 \times CH_2$), 1.03–1.06 (m, 2H, CH_2), 0.87 (t, $J = 6.6$ Hz, 6H, $2 \times CH_3$); ^{13}C NMR δ 157.1 (C_{Ar} IV°), 129.7 (C_{Ar}), 129.0 (C_{Ar} IV°), 127.9 (C_{Ar}), 120.1 (C_{Ar}), 110.9 (C_{Ar}), 67.9 (CH_2O), 60.7 (*C*HN), 46.1 (CH_AH_B), 31.9 (CH_2), 31.4 (CH_2), 29.44 (CH_2), 29.37 (CH_2), 29.36 (CH_2), 26.2 (CH_2), 25.1 (CH_2), 22.7 (CH_2), 14.2 (CH_3). HRMS (ESI, $[M+H]^+$) calcd for $[C_{36}H_{58}N_2O_2+H]^+$ 551.4571; found 551.4579.

4.2.4. Compound 1i

Ligand **1i** was prepared according to the general procedure starting from (1*R*,2*R*)-(+)-1,2-diaminocyclohexane L-tartrate salt (1.52 g, 5.75 mmol). Part of the imine (536 mg, 1.49 mmol) was reduced to afford 511 mg (93% yield after two stages) of the desired product as a light yellow oil, $R_f = 0.40$ ($CHCl_3$/EtOH, 20:1, v/v), $[\alpha]_D = -62.0$ (*c* 0.5, MeOH); IR (film): ν_{max} 3296, 3065, 2928, 2855, 1572, 1445, 1126, 1038, 1049, 751 cm^{-1}; ^1H NMR δ 7.39 (dd, $J = 7.2$ Hz, 2.0 Hz, 2H, ArH), 7.30 (dd, $J = 7.2$, 2.0 Hz, 2H, ArH), 7.12–7.22 (m, 4H, ArH), 3.95 (d, $J = 13.8$ Hz, 2H, CH_AH_B), 3.74 (d, $J = 13.8$ Hz, 2H, CH_AH_B), 2.23–2.27 (m, 2H, $2 \times CHN$), 2.16 (br d, $J = 13.2$ Hz, 2H, CH_2), 2.02 (br s, 2H, $2 \times NH$), 1.70–1.73 (m, 2H, CH_2), 1.19–1.26 (m, 2H, CH_2), 1.03–1.10 (m, 2H, CH_2). ^{13}C NMR δ 138.5 (C_{Ar} IV°), 133.8 (C_{Ar} IV°), 130.0 (C_{Ar}), 129.4 (C_{Ar}), 128.1 (C_{Ar}), 126.8 (C_{Ar}), 61.1 (CHN), 48.4 (CH_AH_B), 31.7 (CH_2), 25.1 (CH_2). HRMS (ESI, $[M+H]^+$) calcd for $[C_{20}H_{24}N_2Cl_2+H]^+$ 363.1389; found 363.1374.

4.2.5. Compound 1j

Ligand **1j** was prepared according to the general procedure starting from (1*R*,2*R*)-(+)-1,2-diaminocyclohexane L-tartrate salt (1.32 g, 5.0 mmol). Part of the imine (500 mg, 1.39 mmol) was reduced to afford 494 mg (92% yield) of the desired product as a light yellow solid, mp = 53–55 °C; $R_f = 0.36$ ($CHCl_3$/EtOH, 20:1, v/v), $[\alpha]_D = -53$ (*c* 0.5, MeOH); IR (film): ν_{max} 3301, 3062, 2928, 2855, 1597, 1575, 1458, 1200, 1117, 868, 778, 683 cm^{-1}; ^1H NMR δ 7.30 (s, 2H, ArH), 7.16–7.25 (m, 6H, ArH), 3.85 (d, $J = 13.5$ Hz, 2H, CH_AH_B), 3.61 (d, $J = 13.5$ Hz, 2H, CH_AH_B), 2.20–2.23 (m, 2H, $2 \times CHN$), 2.09–2.14 (m, 2H, CH_2), 1.85 (br s, 2H, $2 \times NH$), 1.69–1.73 (m, 2H, CH_2), 1.18–1.24 (m, 2H, CH_2), 0.99–1.06 (m, 2H, CH_2); ^{13}C NMR δ 143.3 (C_{Ar} IV°), 134.2 (C_{Ar} IV°), 129.7 (C_{Ar}), 128.1 (C_{Ar}), 127.0 (C_{Ar}), 126.2 (C_{Ar}), 61.0 (CHN), 50.4 (CH_AH_B), 31.7 (CH_2), 25.1 (CH_2). HRMS (ESI, $[M+H]^+$) calcd for $[C_{20}H_{24}N_2Cl_2+H]^+$ 363.1389; found 363.1389.

4.2.6. Compound 1k

Ligand **1k** was prepared according to the general procedure starting from (1*R*,2*R*)-(+)-1,2-diaminocyclohexane L-tartrate salt (778 mg, 2.95 mmol). Imine (1.014 g, 2.82 mmol) was reduced affording 884 mg (83% after two stages) of the desired product as a light yellow oil, $R_f = 0.32$ ($CHCl_3$/EtOH, 20:1, v/v), $[\alpha]_D = -46.2$ (*c* 0.5, MeOH); IR (film): ν_{max} 3299, 3027, 2928, 2854, 1597, 1490, 1457, 1091, 1015, 800 cm^{-1}; ^1H NMR δ 7.22 (AB system, $J = 14.6$, 8.6 Hz, 8H, ArH), 3.83 (d, $J = 13.3$ Hz, 2H, CH_AH_B), 3.59 (d, $J = 13.3$ Hz, 2H, CH_AH_B), 2.18–2.21 (m, 2H, $2 \times CHN$), 2.11 (br d, $J = 13.2$ Hz, 2H, CH_2), 1.84 (s, 2H, $2 \times NH$), 1.69–1.71 (m, 2H, CH_2), 1.16–1.23 (m, 2H, CH_2), 0.98–1.01 (m, 2H, CH_2); ^{13}C NMR δ 139.7 (C_{Ar} IV°), 132.5 (C_{Ar} IV°), 129.4 (C_{Ar}), 128.5 (C_{Ar}), 60.9 (CHN), 50.2 (CH_AH_B), 31.6 (CH_2), 25.1 (CH_2). HRMS (ESI, $[M+H]^+$) calcd for $[C_{20}H_{24}N_2Cl_2+H]^+$ 363.1389; found 363.1371.

4.2.7. Compound 1l

Diamine **1l** was prepared by the reduction of the corresponding diimine.[16]

The diimine (428 mg, 1.0 mmol, 1.0 equiv) was suspended in MeOH (5.0 mL) after which $NaBH_4$ (190 mg, 5.0 mmol, 5.0 equiv) was added portionwise for 10 min at rt, which caused gas liberation. After 24 h, water was added (10 mL), the resulting mixture was stirred for 5 min and the solvents were evaporated in vacuo. The residue was treated with CH_2Cl_2 (10 mL) and brine (10 mL), phases were separated and water layer was washed with CH_2Cl_2 (5×5 mL). Combined organic fractions were dried (K_2CO_3), and solvent was evaporated giving 379 mg (88% yield) of white

crystals. Analytical sample was obtained by crystallization from CH_2Cl_2/*n*-hexane, mp = 156–157 °C; $[\alpha]_D = -36.2$ (*c* 0.9, EtOH); IR (KBr): ν_{max} 3280, 2919, 2851, 1561, 1471, 1436, 1114, 1087, 849, 776, 762 cm^{-1}; ^1H NMR δ 7.24 (d, *J* = 7.8 Hz, 4H, ArH), 7.08 (t, *J* = 7.8 Hz, 2H, ArH), 4.11 (d, *J* = 12.3 Hz, 2H, CH_AH_B), 3.90 (d, *J* = 12.3 Hz, 2H, CH_AH_B), 2.26 (br d, *J* = 12.9 Hz, 2H, CH_2), 2.16–2.19 (m, 2H, 2 × C*H*N), 2.04 (br s, 2H, 2 × N*H*), 1.72–1.75 (m, 2H, CH_2), 1.18–1.32 (m, 2H, CH_2), 0.97–1.10 (m, 2H, CH_2); ^{13}C NMR δ 136.6 (C_{Ar} IV°), 136.1 (C_{Ar} IV°), 128.6 (C_{Ar}), 128.2 (C_{Ar}), 61.2 (CHN), 46.1 (CH_AH_B), 32.1 (CH_2), 25.2 (CH_2). HRMS (ESI, $[M+H]^+$) calcd for $[C_{20}H_{22}N_2Cl_4+H]^+$ 431.0610; found 431.0620.

4.2.8. Compound 1m

Ligand **1m** was prepared according to the general procedure starting from (1*R*,2*R*)-(+)-1,2-diaminocyclohexane L-tartrate salt (673 mg, 2.5 mmol). Part of the imine (355 mg, 0.74 mmol) was reduced to afford 346 mg (85% yield afer two stages) of the desired product as a light yellow oil, R_f = 0.57 ($CHCl_3$/EtOH, 20:1, v/v), $[\alpha]_D = -43.9$ (*c* 0.5, MeOH); IR (film): ν_{max} 3294, 3061, 2928, 2854, 2567, 1440, 1123, 1109, 1025, 749 cm^{-1}; ^1H NMR δ 7.49 (d, *J* = 7.9 Hz, 2H, ArH), 7.40 (d, *J* = 7.2 Hz, 2H, ArH), 7.23 (t, *J* = 7.2 Hz, 2H, ArH), 7.07 (dt, *J* = 7.9, 1.2 Hz, 2H, ArH), 3.94 (d, *J* = 13.8 Hz, 2H, CH_AH_B), 3.73 (d, *J* = 13.8 Hz, 2H, CH_AH_B), 2.25–2.28 (m, 2H, 2 × C*H*N), 2.17 (br d, *J* = 12.9 Hz, 2H, CH_2), 2.09 (s, 2H, 2 × N*H*), 1.71–1.73 (m, 2H, CH_2), 1.90–1.27 (m, 2H, CH_2), 1.03–1.11 (m, 2H, CH_2); ^{13}C NMR δ 140.0 (C_{Ar} IV°), 132.7 (C_{Ar}), 130.2 (C_{Ar}), 128.4 (C_{Ar}), 127.4 (C_{Ar}), 124.1 (C_{Ar} IV°), 61.1 (CHN), 50.9 (CH_AH_B), 31.7 (CH_2), 25.1 (CH_2). HRMS (ESI, $[M+H]^+$) calcd for $[C_{20}H_{24}N_2Br_2+H]^+$ 451.0379; found 451.0395.

4.2.9. Compound 1o

Ligand **1o** was prepared from diamine **1n** according to the literature procedure.[8]

Iodomethane (120 mg, 0.8 mmol, 2.0 equiv) was added to solution of **1n** (193 mg, 0.4 mmol, 1.0 equiv) in dichloromethane (2.0 mL), and the resulting mixture was stirred for 4 h at rt. The first portion of $LiOH·H_2O$ (17 mg, 1.0 equiv) was added that resulted in clouding of the reaction mixture. The second portion of $LiOH·H_2O$ (17 mg, 1.0 equiv) was added, stirring was continued for 16 h and water (10 mL) was added. Phases were separated, water layer was washed with CH_2Cl_2 (3 × 5 mL) and combined organic fractions were dried (K_2CO_3). Solvent was evaporated giving 201 mg of colorless oil. The product was purified by column chromatography on silica gel (20 g, $CHCl_3$/EtOH, 10:1, v/v) affording the desired product 106 mg (53%) as a light yellow oil; R_f = 0.16 ($CHCl_3$/EtOH, 20:1, v/v), $[\alpha]_D = +10.9$ (*c* 1.64, CH_2Cl_2); IR (film): ν_{max} 3041, 3022, 2930, 2855, 2788, 1699, 1669, 1599, 1486, 1449, 1402, 1068, 1011, 833, 816, 798, 478 cm^{-1}; ^1H NMR δ 7.38 (d, *J* = 8.1 Hz, 4H, ArH), 7.22–7.24 (m, 4H, ArH), 3.65–3.70 (m, 2H, CH_AH_B), 3.52 (d, *J* = 13.2 Hz, 2H, CH_AH_B), 2.56–2.59 (m, 2H, 2 × C*H*N), 2.17 (s, 6H, 2 × CH_3), 1.90 (br d, *J* = 12 Hz, 2H, CH_2), 1.72–1.75 (m, 2H, CH_2), 1.10–1.24 (m, 4H, 2 × CH_2); ^{13}C NMR δ 139.9 (C_{Ar} IV°), 131.2 (C_{Ar}), 130.6 (C_{Ar}), 120.4 (C_{Ar} IV°), 63.8 (CHN), 57.8 (CH_AH_B), 36.3 (CH_3), 25.8 (CH_2), 25.5 (CH_2). HRMS (ESI, $[M+H]^+$) calcd for $[C_{22}H_{28}N_2Br_2+H]^+$ 479.0692; found 479.0690.

4.2.10. Complex 2

Complex **2** was prepared according to the literature procedure.[3h]

The solution of ligand **1k** (391 mg, 1.08 mmol, 1.0 equiv) in EtOH (25 mL, distilled with CaH_2 before use) was treated with copper(II) acetate hydrate (199 mg, 1.0 equiv). After a few seconds, the color changed to deep blue, and the residue disappeared. The mixture was stirred for 18 h at rt, solvent was removed in vacuo, and the amorphous solid was dried in a vacuum pump for 2 h. Then, the crude complex was dissolved in hot CH_2Cl_2 and treated with *n*-hexane. Crystals are formed after 2 h of standing at rt. Resulting solid was filtered, washed with *n*-hexane, and dried giving 358 mg (61%) of blue crystals; $[\alpha]_D = +475$ (*c* 0.016, CH_2Cl_2); IR (KBr): ν_{max} 3220, 3176, 2935, 2860, 1616, 1583, 1493, 1393, 1332, 1094, 805, 668, 615, 494, 483, 325, 301 cm^{-1}; Anal. Calcd for $C_{24}H_{30}Cl_2CuN_2O_4·0.5H_2O$: C 51.29; H 5.56; N 4.98. Found C 51.09; H 5.35; N 4.98.

4.3. General procedure for catalytic Henry reaction

Ligand (0.06 mmol, 12 mol %) and $Cu(OAc)_2·nH_2O$ (10.0 mg, 0.05 mmol, 10 mol %) were treated with ethanol (96% aq, 1.0 mL), and the resulted deep blue to green solution was stirred for 1.0 h at 23 °C without any other precautions. Then a solution of respective aldehyde (0.5 mmol, 1.0 equiv) in ethanol (0.5 mL) was added, the reaction mixture was cooled to 0 °C (ice-water bath), stirred for 15 min. followed by addition of CH_3NO_2 (270 μL, 5.0 mmol, 10 equiv) via syringe. After 48 h, the cold reaction mixture was put into a plug of silica gel (30g, *n*-hexane/AcOEt 6:1,v/v) and afforded the desired β-nitroalcohol. Products were analyzed by ^1H NMR ($CDCl_3$), and measurement of specific rotations in CH_2Cl_2 or $CHCl_3$ was determined. Enantiomeric excess was determined using HPLC on Chiracel OD-H or Chiralpak AD-H chiral columns (flow rate: 1.0 mL/min, λ = 225 nm). Reported values are listed below:

(*S*)-(+)-1-Phenyl-2-nitroethane-1-ol: Chiracel OD-H, *n*-hexane/*i*-PrOH, 9:1, t_{minor} = 13.8 min, t_{major} = 16.6 min.

(*S*)-(+)-1-(4-Chlorophenyl)-2-nitroethane-1-ol: Chiracel OD-H, *n*-hexane/*i*-PrOH, 9:1, t_{minor} = 13.9 min, t_{major} = 17.3 min.

(*S*)-(+)-1-Cyclohexyl-2-nitroethane-1-ol: Diacel Chiralpak AD-H, *n*-hexane/*i*-PrOH, 9:1, t_{minor} = 8.8 min, t_{major} = 9.4 min.

(*S*)-(+)-1-(2-Methoxyphenyl)-2-nitroethane-1-ol: Chiracel OD-H, *n*-hexane/*i*-PrOH, 9:1, t_{minor} = 11.3 min, t_{major} = 13.3 min.

(*S*)-(+)-1-(4-Nitrophenyl)-2-nitroethane-1-ol: Chiracel OD-H, *n*-hexane/*i*-PrOH, 4:1, t_{minor} = 12.0 min, t_{major} = 14.4 min.

(+)-1-(2-Naphthyl)-2-nitroethane-1-ol: Chiracel OD-H, *n*-hexane/*i*-PrOH, 4:1, t_{minor} = 20.3 min, t_{major} = 27.6 min.

(+)-1-(1-Naphthyl)-2-nitroethane-1-ol: Chiracel OD-H, *n*-hexane/*i*-PrOH, 4:1, t_{minor} = 9.7 min, t_{major} = 14.4 min.

(*S*)-(+)-1-Nitro-4-phenyl-3-buten-2-ol: Chiracel OD-H, *n*-hexane/*i*-PrOH, 4:2, t_{major} = 17.5 min, t_{minor} = 19.8 min.

(+)-1-(2-Furanyl)-2-nitroethane-1-ol: Chiralpak AD-H, *n*-hexane-*i*PrOH, 95:5, t_{minor} = 21.9 min, t_{major} = 23.1 min.

(*S*)-(+)-1-*tert*-Butyl-2-nitroethane-1-ol: Chiralcel OD-H, *n*-hexane-*i*PrOH, 95:5, t_{minor} = 16.7 min, t_{major} = 18.8 min.

(*S*)-(+)-1-(3-Chlorophenyl)-2-nitroethane-1-ol: OD-H, *n*-hexane/*i*-PrOH, 9:1, t_{minor} = 14.0 min, t_{major} = 17.9 min.

(*S*)-(+)-1-(4-Phenylphenyl)-2-nitroethanol: OD-H, *n*-hexane/*i*-PrOH, 9:1, t_{minor} = 11.3 min, t_{major} = 13.0 min.

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