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Application of chiral *N*,*N*′-dialkyl-1,2-cyclohexanediamine derivatives in asymmetric copper(II)-catalyzed Henry reactions

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ABSTRACT

A series of chiral *N*,*N*′-dialkyl-1,2-cyclohexanediamine derivatives were designed, synthesized, and applied as ligands in asymmetric copper(II)-catalyzed Henry reactions. The catalysts based on such ligands and copper(II) acetate were found to promote asymmetric Henry reactions between aromatic/aliphatic aldehydes and nitromethane efficiently, and could provide the corresponding β-nitroalcohols in very good yields and with enantioselectivities of up to 93.6%.

1. Introduction

The Henry reaction is a powerful and atom economical C–C bond forming reaction in organic chemistry,[1] which has been widely developed and applied in the field of synthetic chemistry. The resulting β-nitroalcohols are usually transformed into valuable intermediates of organic synthesis, such as 1,2-amino alcohols, α-hydroxyl carboxylic acids, and the preparation of some drugs.[2–4] The first asymmetric version of the Henry reaction was reported by Shibasaki in 1992.[5] After that, a variety of metal/chiral ligand complexes and organocatalytic appeared in reports regarding the catalytic asymmetric Henry reaction.[6,7] Generally, the corresponding catalytic reactions are mainly divided into three categories, namely, metal/chiral ligand complex-based reactions, organocatalytic reactions, and enzymatic catalysis.[8] Metal based chiral catalysts[9] mainly include rare earth-BINOL complexes, dinuclear Zn catalysts, Cu-bis(oxazoline) (BOX) complexes, and so on, while organocatalysts are mainly concerned with cinchona alkaloids, chiral thioureas, and guanidines;[10] and hydroxynitrile lyase, transglutaminase (TGase), and *Candida cylindracea* Lipase (CCL) belonged to the enzymatic catalysis.[11,12] In recent years, many researchers such as Trost,[13] Evans,[14] Palomo,[15] and Jørgensen[16] have studied various metal based catalysts containing chiral ligands, which have been applied in catalytic Henry reactions of aromatic aldehydes with significantly high enantioselectivity.[17–19] Usually, substrates such as benzaldehyde, substituted aromatic aldehydes, and heterocyclic aromatic aldehydes are often used to obtain the corresponding β-nitroalcohols, which can be used to prepare medicines such as (*R*)-denopamine,[20] (*R*)-pronethalol,[21] and so on.

So far, the application of these catalysts is very limited in catalytic Henry reactions concerned with aromatic aldehydes. To the best of our knowledge, only several research groups have reported on the asymmetric Henry reactions of aliphatic aldehydes.[22] The resulting β-nitroalcohols obtained by asymmetric Henry reaction of aliphatic aldehydes have been widely applied in the field of synthetic chemistry. For example, some alkyl-substituted nitro alcohols can provide succinic anhydride;[23] nitroolefins which were gained by dehydration of nitroalcohols are an important intermediate for the pharmaceutical industry;[24] and cyclohexyl nitro alcohol is prepared by melanocortin as a starting material.[25] So far, only several catalytic systems are feasible for both aromatic and aliphatic aldehydes.[26–28] Therefore, the development of asymmetric catalysis for various aliphatic aldehyde reactions is still in great demand.

Recently, we have been interested in developing *trans*-1,2-cyclohexanediamine derivatives that can be applied in asymmetric catalytic reactions.[29,30] Herein we report a number of chiral *N*,*N*′-dialkyl-1,2-cyclohexanediamine derivatives (Scheme 1), which could be suitable as ligands with copper(II) acetate and applied in asymmetric Henry reactions involved with aliphatic aldehydes.

2. Results and discussion

The reaction between benzaldehyde and nitromethane was chosen as the model reaction since aliphatic aldehydes as substrates are seldom systematically studied.[21] Asymmetric Henry reactions were investigated by using different ligands **1a**–**1n** (Scheme 1) in the presence of $Cu(OAc)_2$, and the results are summarized in Table 1. The results indicated that the diamine derivatives with different alkyl groups had a great influence on the enantioselectivity and the yield of the product. Ligands with linear alkyl chains **1b**, **1d**, and **1g** gave products with up to 88.6% ee.

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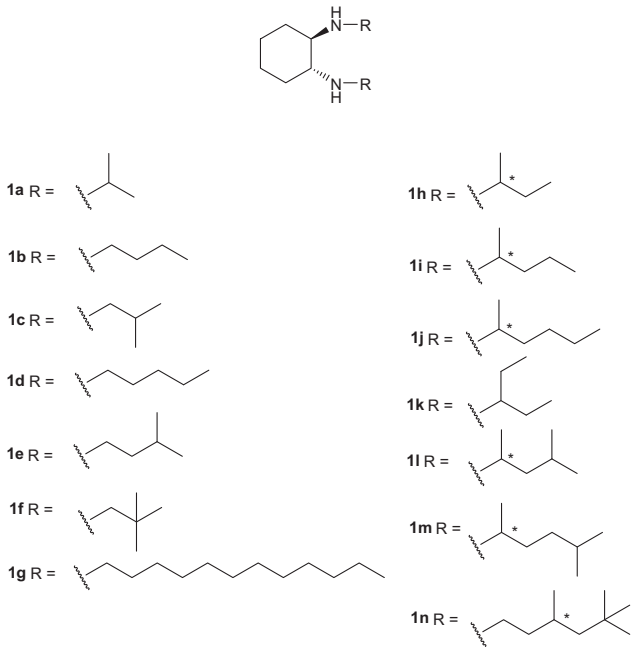
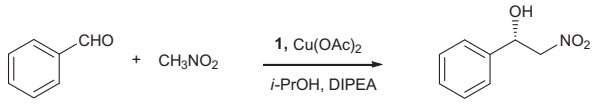


Scheme 1. Structure of ligand **1**.

Table 1
Screening of catalysts with 1,2-diamine derivatives as ligands in the Henry reaction between benzaldehyde and nitromethane[a]



2a 3a

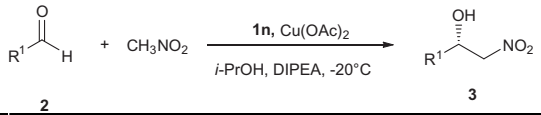
Entry	Ligand	Yield[b] (%)	ee[c] (%)
1	**1a**	70.7	17.1
2	**1b**	98.2	85.7
3	**1c**	99.0	78.1
4	**1d**	97.3	86.8
5	**1e**	93.8	90.0
6[d]	**1f**	95.9	−39.4
7	**1g**	97.2	88.6
8	**1h**	95.8	78.6
9	**1i**	99.0	79.9
10	**1j**	90.5	76.6
11	**1k**	74.5	70.9
12	**1l**	94.3	78.4
13	**1m**	90.9	79.9
14	**1n**	91.7	93.6

[a] Reactions were carried out on a 0.5 mmol scale of benzaldehyde with 10 equiv of CH_3NO_2 in *i*-PrOH, 12 mol % of the corresponding ligand **1a**–**1o**, 10 mol % of $Cu(OAc)_2{\cdot}H_2O$, 7.7 mol % of DIPEA at −20 °C for 48 h.
[b] Yield of the isolated product.
[c] Enantiomeric excess was determined by HPLC analysis using Chiralpak IC as a column; the absolute configuration was established as the (*S*)-enantiomer by comparison with the literature data.[22,31]
[d] The absolute configuration of entry 6 was established as the (*R*)-enantiomer by comparison with the literature data.[22,31]

Increasing the number of carbon atoms in the unbranched alkyl groups lightly enhanced the enantioselectivities (Table 1, entries 2, 4, and 7). When methyl groups were introduced at the end position of the alkyl chain such as in **1c**, **1e**, **1l**, **1m**, and **1n**, high ee values of the product with a maximum of 93.6% with **1n** were achieved. However, when a methyl group was located near the nitrogen atom such as in **1a**, **1h**, **1i**, and **1j**, moderate ee values of the product ranging from 17.1% for **1a** to 79.9% for **1i** were obtained. This may be due to the alkyl substituents being less bulky. These results proved that the branched alkyl groups at the end-position **1e**, **1n** could promote the reaction with a higher enantioselectivity compared to those at a neighboring position to the nitrogen atom in ligand **1a**. Ligand **1f** had an opposite catalytic effect on such a reaction with a minus ee value. Therefore, **1n** was selected for further research.

In order to examine the scope of the asymmetric Henry reaction with our ligands, we applied **1n** (12 mol %) with $Cu(OAc)_2{\cdot}H_2O$ (10 mol %) in *i*-PrOH to the nitroaldol reaction of various aliphatic aldehydes (Table 2, entries 1–9) and aromatic aldehydes (Table 2, entries 10–24).[31] A variety of aliphatic aldehydes were obtained in high yields (up to 98%) and with excellent enantioselectivities ranging from 91.0% to 93.8%, which produced their respective β-nitroalcohols. It should be noted that the length and size of the alkyl chains in the substrates, no matter if they were unbranched (Table 2, entries 1, 2, 4, 7, and 8), branched (Table 2, entries 3, 5, and 6) alkyl chain aldehydes or cyclohexanealdehyde (Table 2, entry 9), had hardly any influence on the enantioselectivity or the yield of the resulting product derived from aliphatic aldehydes. The scope of our catalyst system was also extended to aromatic aldehydes (entries 10–24), which provided high yields (up to 96%) and excellent enantioselectivities (up to 92.7% ee) as well. A variety of 2-, 3-, or 4-substituted benzaldehydes (entries 10–17) were involved with the corresponding reactions and no significant differences in the yields or enantioselectivities of the products related were observed. This indicated that the position of the substituted groups on the phenyl ring had little influence on the catalytic

Table 2
Henry reactions of aldehydes with nitromethane catalyzed by $Cu(OAc)_2$ with **1n**[a]



2 3

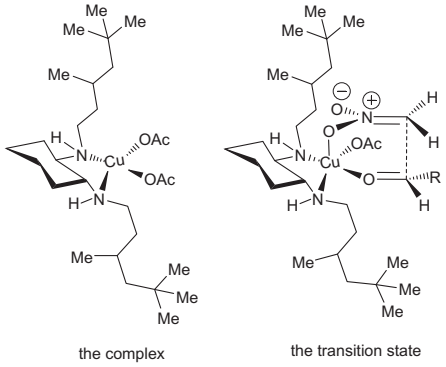
Entry	R^1	Yield[b] (%)	ee[c] (%)
1	CH_3CH_2 **2b**	98.1	92.6
2	$CH_3CH_2CH_2$ **2c**	93.7	92.3
3	$(CH_3)_2CH_2$ **2d**	97.2	93.6
4	$CH_3(CH_2)_2CH_2$ **2e**	94.6	93.4
5	$(CH_3)_2CHCH_2$ **2f**	98.6	91.0
6	$(CH_3)_3C$ **2g**	92.7	93.2
7	$CH_3(CH_2)_3CH_2$ **2h**	95.6	91.8
8	$CH_3(CH_2)_4CH_2$ **2i**	93.7	92.1
9	Cyclohexyl **2j**	96.2	91.6
10	2-$NO_2C_6H_4$ **2k**	93.2	90.1
11	3-$NO_2C_6H_4$ **2l**	94.9	81.8
12	4-$NO_2C_6H_4$ **2m**	93.6	85.1
13	2-ClC_6H_4 **2n**	91.7	93.8
14	3-ClC_6H_4 **2o**	93.0	87.2
15	4-ClC_6H_4 **2p**	91.2	87.2
16	2-$MeOC_6H_4$ **2q**	92.7	81.0
17	3-$MeOC_6H_4$ **2r**	96.8	90.9
18	4-MeC_6H_4 **2s**	89.5	75.1
19	4-FC_6H_4 **2t**	94.1	86.7
20	4-PhC_6H_4 **2u**	83.6	84.2
21	PhCH=CH **2v**	93.6	84.1
22	2-Furyl **2w**	95.4	91.2[d]
23	1-Naphthyl **2x**	92.8	84.5
24	2-Naphthyl **2y**	89.3	92.7

[a] Reactions were performed on a 0.5 mmol scale of aldehydes with 10 equiv of nitromethane in a mixture of 1.0 mL of *i*-PrOH, 12 mol % ligand **1n**, and 10 mol % $Cu(OAc)_2{\cdot}H_2O$ in the presence of 7.7 mol % DIPEA at −20 °C for 48 h.
[b] Yield of isolated product.
[c] Enantiomeric excess was determined by HPLC analysis using Chiracel OD-H, Chiralpak AD-H, and Chiralpak AS-H as columns; the absolute configuration was established as the (*S*)-enantiomer by comparison with the literature data.[22,31]
[d] The absolute configuration of **3w** was established as the (*R*)-enantiomer by comparison with the literature data.[22,31]

effect of our system. It can be seen in entries 12, 15, 18, 19, and 20 that high yields (more than 91.7%) and good enantioselectivities (ee from 85.1% to 90.9%) of the products can be achieved when the substituent is an electron-withdrawing group; however, the enantioselectivity of the products decreased when the substituent was an electron-donating group. This demonstrates that the electronic character of the substituent has a definite effect on the enantioselectivity of the product. In addition, some larger aromatic aldehydes such as 1-naphthaldehyde and 2-naphthaldehyde (entries 23 and 24) also provided their respective β-nitroalcohols with good to high yields (up to 95.4%) and with enantioselectivities ranging from 84.5% to 92.7%.

To further apply our catalyst system in other reactions, an asymmetric synthesis of (*S*)-(+)-denopamine **6**[32] (Scheme 2) which could be prepared via an asymmetric nitroaldol reaction was studied. Ligand **1n** was found to promote an efficient synthesis of the β-adrenoceptor agonists (−)-denopamine enatiomer [(*S*)-(+)-denopamine] in the catalytic enantioselective nitroaldol reaction.[33] As expected, the catalyst consisting of **1n**/$Cu(OAc)_2$ gave the desired product **5** with up to 92.9% ee and 68.1% yield (Scheme 3).

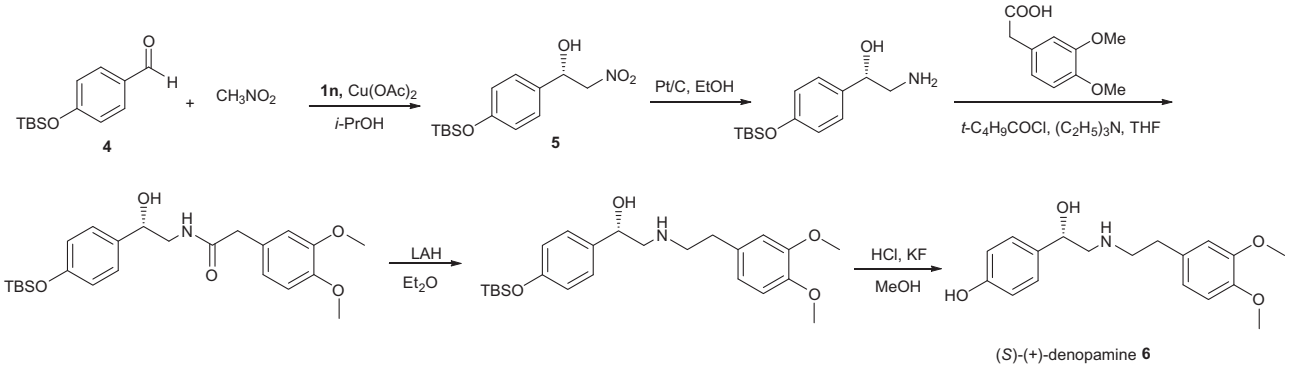
Based on the generally accepted model proposed by Jørgensen[34] and Kodama,[35] we here propose a possible model of the catalytic cycle transition state for our asymmetric Henry reaction (Scheme 4). First of all, the complex was formed from ligand **1n** and $Cu(OAc)_2$. Due to Jahn–Teller distortion, the Cu(II) complex with an octahedral geometry has four strong coordination sites at the equatorial positions and two weak coordination sites at the apical positions. Two neighboring strong coordination sites were occupied by the two nitrogen atoms of **1n**, forming the complex. Secondly, under the coordination influence of the complex, the substituents on the two amino groups of **1n** cause an obvious steric hindrance to leave space and provide two weak coordination sites at the apical positions of the metal complex. Both the aldehyde and nitroalkane are efficiently activated by coordination to the equatorial and apical positions of the copper complex, respectively. The nitroalkane approaches from the unoccupied upper side of the copper ion, forming a transition state. The alkyl chains on the two amino groups of **1n** occupy the major space around the transition state to leave only the above space, whereas the aldehyde molecule with less steric hindrance is coordinated to the metal atom via the less-crowded space to give the (*S*)-enantiomer. Compared with aromatic aldehydes, aliphatic aldehydes with less steric hindrance can easily occupy the apical positions of the metal atom. Thus, the products from aliphatic aldehydes were obtained with higher enantioselectivities than those from aromatic aldehydes by the catalyst consisting of a **1n**/$Cu(OAc)_2$ complex.



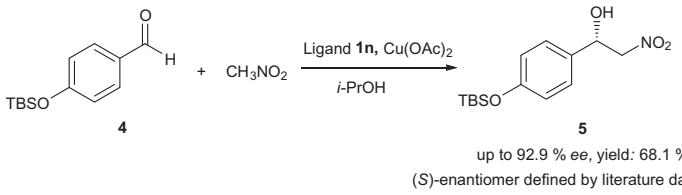
Scheme 4. Proposed transition state of the Henry reaction catalyzed by **1n**/$Cu(OAc)_2$.

3. Conclusion

In conclusion, we have developed a series of chiral *N*,*N*′-dialkyl-1,2-cyclohexanediamine derivatives, which can be used to combine with copper(II) acetate as efficient catalysts for asymmetric Henry reactions. The optimized catalyst of **1n**–$Cu(OAc)_2$ was suitable to efficiently catalyze asymmetric Henry reactions between aliphatic/aromatic aldehydes and nitromethane, to provide β-nitroalcohols in high yields (up to 98.6%) and with high enantiomeric excess (up to 93.6%). In addition to aromatic aldehydes, our



Scheme 2. Asymmetric synthesis of (*S*)-(+)denopamine.



Scheme 3. Henry reactions of aldehyde **4** and nitromethane in the presence of **1n** with copper(II) acetate.

catalyst system can also be used to prepare β-nitroalchohols with excellent enantioselectivities and high yields for a broad range of aliphatic aldehydes.

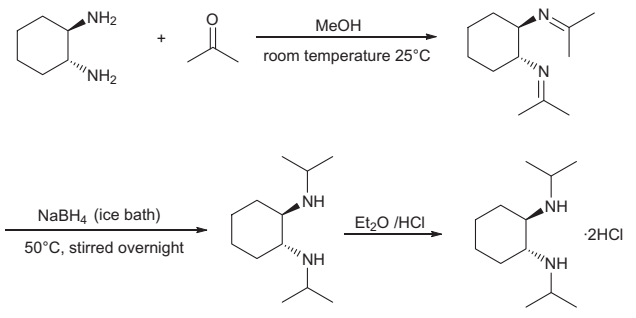
4. Experimental

4.1. General

All reagents, such as aldehydes, isopropanol, nitromethane, and copper acetate monohydrate, were purchased commercially and used without further purification. Infrared spectra were measured on KBr pellets on a Nicolet IR200 FT-IR spectrometer in the range of 4000–400 cm^{-1}; Mass spectra were measured on an Agilent Accurate Mass 6224 TOF LC/MS system; NMR spectra were recorded at 300 or 500 MHz for ^1H and at 75 MHz for ^{13}C in deuterated water. The corresponding products were separated by column chromatography on silica gel. Enantiomeric excesses (ee) were obtained by HPLC on chiral columns (IC, OD-H, AS-H or AD-H), and elution with *n*-hexane-*i*-PrOH.

4.2. Ligands

The synthetic process for ligand **1** (Scheme 5) is as follows. (1*R*,2*R*)-DACH (10 mmol) in MeOH (30 mL) was mixed with the corresponding aldehyde or ketone (30 mmol). After the mixture was kept for 2 h at room temperature, it was cooled in an ice-water bath, followed by the slow addition of $NaBH_4$ (1.5 g), and kept stirring overnight at 50 °C. Next, 5 mL of water was added to quench the reaction, after which water (30 mL) was added and the aqueous phase was extracted with EtOAc (30 mL × 3). The combined organic extracts were washed with a saturated NaCl solution and dried over anhydrous Na_2SO_4. By concentrating the solution in vacuo, the crude product was obtained. A solution of HCl/Et_2O (1 mol/L, 20 mL) was slowly added with stirring to the solution of the crude product in absolute ether (75 mL), and the resulting white solid was filtered off, washed with ether, and dried in vacuo to yield up to 90%. The product was obtained as a dihydrochloride salt **1**·2HCl. The dihydrochloride salt was confirmed by testing the weight of AgCl deposits when the quantitative salt was treated with $AgNO_3$ in its aqueous solution.



Scheme 5. Synthetic process for ligand **1** (with **1a** as an example).

Among the ligands prepared, it was noted that new stereogenic centers in **1h**, **1i**, **1j**, **1l**, **1m**, or **1n** would be generated when the branched alkyl groups were linked to the nitrogen atoms of (1*R*,2*R*)-DACH. The corresponding proton NMR spectroscopic data suggested that the resulting ligands were mixtures of two diastereomers, which were used directly as catalysts without resolution.

4.2.1. (1*R*,2*R*)-*N*^{1},*N*^{2}-Diisopropylcyclohexane-1,2-diamine dihydrochloride 1a·2HCl

According to the general procedure, **1a**·2HCl was obtained as a white solid. Yield: 76%. $[\alpha]_D^{25} = -25.8$ (*c* 0.47, H_2O). ^1H NMR (500 MHz, D_2O, 25 °C) *δ*: 1.38 (d, 12H, CH*CH*$_3$), 1.49–2.29 (m, 8H, CH_2 of DACH), 3.45–3.50 (m, 2H, NHC*H*CH$_3$), 3.66–3.71 (m, 2H, NH*CH*). ^{13}C NMR (D_2O, 75 MHz) *δ*: 22.91, 25.14, 25.37, 27.02, 27.88, 31.97, 33.53, 44.88, 52.71, 55.50, 60.79, 61.27. IR: *ν* = 3465, 3320, 3220, 2961, 2804, 1577, 1466, 1389, 1375, 1072, 509 cm^{-1}. HRMS (ESI): Calcd for $C_{12}H_{27}N_2$ $[M+H]^+$ 199.2169, Found: 199.2161.

4.2.2. (1*R*,2*R*)-*N*^{1},*N*^{2}-Dibutylcyclohexane-1,2-diamine dihydrochloride 1b·2HCl

According to the general procedure, **1b**·2HCl was obtained as a white solid. Yield: 82%. $[\alpha]_D^{25} = -56.9$ (*c* 0.5, H_2O). ^1H NMR (300 MHz, D_2O, 25 °C) *δ*: 0.99 (t, *J* = 4.1 Hz, 6H, CH_2CH_3), 1.18–1.51 (m, 8H, CH_2CH_3), 1.38–2.38 (m, 8H, CH_2 of DACH), 3.07–3.17 (m, 2H, NH*CH*), 3.55–3.57(m, 4H, NHCH_2). ^{13}C NMR (D_2O, 75 MHz) *δ*: 15.44, 21.84, 22.06, 24.35, 25.26, 25.36, 28.28, 29.06, 30.25, 33.01, 48.26, 51.61, 53.15, 59.87. IR: *ν* = 3344, 2960, 2871, 2786, 1594, 1464, 1396, 1004 cm^{-1}. HRMS (ESI): Calcd for $C_{14}H_{31}N_2$ $[M+H]^+$ 227.2482, Found: 227.2490.

4.2.3. (1*R*,2*R*)-*N*^{1},*N*^{2}-Diisobutylcyclohexane-1,2-diamine dihydrochloride 1c·2HCl

According to the general procedure, **1c**·2HCl was obtained as a white solid. Yield: 54%. $[\alpha]_D^{25} = -78.3$ (*c* 0.53, H_2O). ^1H NMR (300 MHz, D_2O, 25 °C) *δ*: 0.96 (d, *J* = 6.2 Hz, 12H, CH*CH*$_3$), 1.39–1.93 (m, 8H, CH_2 of DACH), 2.40–2.44 (m, 2H, CH_2*CH*CH$_3$), 3.13–3.20 (m, 2H, NH*CH*), 3.50–3.59 (m, 4H, NHCH_2). ^{13}C NMR (D_2O, 75 MHz) *δ*: 21.64, 21.99, 24.87, 28.45, 28.76, 55.43, 60.90. IR: *ν* = 3499, 2957, 2773, 1584, 1468, 1371, 1003 cm^{-1}. HRMS (ESI): Calcd for $C_{14}H_{31}N_2$ $[M+H]^+$ 227.2482, Found: 227.2471.

4.2.4. (1*R*,2*R*)-*N*^{1},*N*^{2}-Dipentylcyclohexane-1,2-diamine dihydrochloride 1d·2HCl

According to the general procedure, **1d**·2HCl was obtained as a white solid. Yield: 63%. $[\alpha]_D^{25} = -54.5$ (*c* 0.55, H_2O). ^1H NMR (300 MHz, D_2O, 25 °C) *δ*: 0.89 (t, *J* = 6.7 Hz, 6H, CH_2CH_3), 1.35–1.57 (m, 12H, CH_2CH_3), 1.71–2.30 (m, 8H, CH_2 of DACH), 2.99–3.08 (m, 2H, NH*CH*), 3.20–3.49 (m, 4H, NHCH_2). ^{13}C NMR (D_2O, 75 MHz) *δ*: 15.65, 15.69, 24.08, 24.31, 25.24, 25.37, 26.72, 27.85, 28.26, 30.45, 30.67, 33.01, 48.45, 51.56, 59.83, 66.32. IR: *ν* = 3434, 2956, 2869, 2779, 1589, 1464, 1378, 1009, 731 cm^{-1}. HRMS (ESI): Calcd for $C_{16}H_{35}N_2$ $[M+H]^+$ 255.2795, Found: 255.2791.

4.2.5. (1*R*,2*R*)-*N*^{1},*N*^{2}-Diisopentylcyclohexane-1,2-diamine dihydrochloride 1e·2HCl

According to the general procedure, **1e**·2HCl was obtained as a white solid. Yield: 68%. $[\alpha]_D^{25} = -53.8$ (*c* 0.5, H_2O). ^1H NMR (300 MHz, D_2O, 25 °C) *δ*: 0.93 (d, *J* = 5.6 Hz, 12H, CH*CH*$_3$), 1.41–1.44 (m, 2H, $CH(CH_3)_2$), 1.63–1.73 (m, 8H, CH_2 of DACH), 1.80–2.32 (m, 4H, CH_2CH_2CH), 3.04–3.11 (m, 2H, NH*CH*), 3.24–3.49 (m, 4H, NHCH_2). ^{13}C NMR (D_2O, 75 MHz) *δ*: 23.86, 24.15, 24.28, 28.01, 28.23, 36.81, 47.07, 59.84. IR: *ν* = 3424, 2957, 2871, 2723, 1470, 1361, 988, 773 cm^{-1}. HRMS (ESI): Calcd for $C_{16}H_{35}N_2$ $[M+H]^+$ 255.2795, Found: 255.2793.

4.2.6. (1*R*,2*R*)-*N*^{1},*N*^{2}-Dineopentylcyclohexane-1,2-diamine dihydrochloride 1f·2HCl

According to the general procedure, **1f**·2HCl was obtained as a white solid. Yield: 81%. $[\alpha]_D^{25} = -70.6$ (*c* 0.44, H_2O). ^1H NMR (500 MHz, D_2O, 25 °C) *δ*: 1.05 (s, 18H, CCH_3), 1.31–2.41 (m, 8H, CH_2 of DACH), 2.96–2.98 (m, 2H, NH*CH*), 3.10–3.53 (m, 4H, NHCH_2). ^{13}C NMR (D_2O, 75 MHz) *δ*: 25.19, 28.89, 29.52, 32.62, 59.57, 61.27. IR: *ν* = 3423, 2953, 2871, 2735, 1562, 1468, 1369, 992 cm^{-1}. HRMS (ESI): Calcd for $C_{16}H_{35}N_2$ $[M+H]^+$ 255.2795, Found: 255.2774.

4.2.7. (1*R*,2*R*)-N^1,N^2-Didodecylcyclohexane-1,2-diamine dihydrochloride 1g·2HCl

According to the general procedure, **1g**·2HCl was obtained as a white solid. Yield: 59%. $[\alpha]_D^{25} = -31.0$ (*c* 0.57, MeOH). ^{1}H NMR (300 MHz, D_2O, 25 °C) δ: 0.86–0.90 (m, 6H, CH_2CH_3), 1.25–1.33 (m, 40H, CH_2CH_3), 1.88–2.09 (m, 8H, CH_2 of DACH), 3.01–3.13 (m, 2H, NHCH), 3.86 (m, 4H, $NHCH_2$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 14.06, 22.65, 23.13, 26.18, 29.12, 29.31, 29.54, 29.61, 31.88, 45.34, 57.41, 76.58, 77.00, 77.43. IR: ν = 3349, 2921, 2850, 2389, 1578, 1473, 1372, 1015, 728 cm^{-1}. HRMS (ESI): Calcd for $C_{30}H_{63}N_2$ $[M+H]^+$ 451.4986, Found: 451.4970.

4.2.8. (1*R*,2*R*)-N^1,N^2-Di-(2-butyl) cyclohexane-1,2-diamine dihydrochloride 1h·2HCl

According to the general procedure, **1h**·2HCl was obtained as a white solid. Yield: 66%. $[\alpha]_D^{25} = -71.4$ (*c* 0.51, H_2O). ^{1}H NMR (300 MHz, D_2O, 25 °C) δ: 0.96 (t, *J* = 7.5 Hz, 6H, CH_2CH_3), 1.02–1.41 (m, 6H, NHCHCH_3), 1.47–2.31 (m, 12H, CH_2CH_3, CH_2 of DACH), 3.49–3.57 (m, 4H, NHCH). ^{13}C NMR (D_2O, 75 MHz) δ: 24.95, 25.08, 26.19, 26.25, 28.39, 28.64, 29.32, 29.44, 31.96, 32.13, 54.34, 54.38, 56.41, 56.44. IR: ν = 3429, 2944, 2818, 1583, 1456, 1393, 1026, 998 cm^{-1}. HRMS (ESI): Calcd for $C_{14}H_{31}N_2$ $[M+H]^+$ 227.2482, Found: 227.2484.

4.2.9. (1*R*,2*R*)-N^1,N^2-Di(2-pentanyl)cyclohexane-1,2-diamine dihydrochloride 1i·2HCl

According to the general procedure, **1i**·2HCl was obtained as a white solid. Yield: 79%. $[\alpha]_D^{25} = -82.3$ (*c* 0.53, H_2O). ^{1}H NMR (300 MHz, D_2O, 25 °C) δ: 0.93 (t, *J* = 7.2 Hz, 6H, CH_2CH_3), 1.34 (d, *J* = 6.3 Hz, 6H, $CHCH_3$), 1.43–2.31 (m, 16H, CH_2CH_3 and CH_2 of DACH), 3.38–3.58 (m, 4H, NHCH). ^{13}C NMR (D_2O, 75 MHz) δ: 15.49, 16.90, 19.06, 19.23, 20.49, 20.78, 24.34, 24.95, 28.57, 28.62, 35.17, 38.22, 55.12, 55.17, 57.18, 57.47. IR: ν = 3433, 2822, 2391, 1582, 1456, 1391, 1025, 994, 744 cm^{-1}. HRMS (ESI): Calcd for $C_{16}H_{35}N_2$ $[M+H]^+$ 255.2975, Found: 255.2800.

4.2.10. (1*R*,2*R*)-N^1,N^2-Di(2-hexanyl)cyclohexane-1,2-diamine dihydrochloride 1j·2HCl

According to the general procedure, **1j**·2HCl was obtained as a white solid. Yield: 65%. $[\alpha]_D^{25} = -67.2$ (*c* 0.58, H_2O). ^{1}H NMR (300 MHz, D_2O, 25 °C) δ: 0.89 (t, *J* = 6.4 Hz, 6H, CH_2CH_3), 1.30–1.39 (m, 6H, $CHCH_3$), 1.53–2.30 (m, 20H, CH_2CH_3 and CH_2 of DACH), 3.55 (m, 4H, NHCH). ^{13}C NMR (D_2O, 75 MHz) δ: 15.73, 16.97, 17.03, 19.29, 24.26, 24.37, 24.48, 24.66, 28.39, 28.58, 29.15, 29.43, 35.80, 35.84, 55.38, 55.46, 57.18, 57.44. IR: ν = 3406, 2955, 2787, 1589, 1467, 1391, 1041, 732 cm^{-1}. HRMS (ESI): Calcd for $C_{18}H_{39}N_2$ $[M+H]^+$ 283.3108, Found: 283.3085.

4.2.11. (1*R*,2*R*)-N^1,N^2-Di(3-pentanyl)cyclohexane-1,2-diamine dihydrochloride 1k·2HCl

According to the general procedure, **1k**·2HCl was obtained as a white solid. Yield: 43%. $[\alpha]_D^{25} = -80.1$ (*c* 0.47, H_2O). ^{1}H NMR (300 MHz, D_2O, 25 °C) δ: 0.92–1.01 (m, 12H, CH_2CH_3), 1.39–2.37 (m, 16H, CH_2CH_3 and CH_2 of DACH), 3.47–3.54 (m, 4H, NHCH). ^{13}C NMR (D_2O, 75 MHz) δ: 10.39, 11.06, 22.83, 24.62, 25.55, 28.77, 57.86, 61.31. IR: ν = 3432, 2966, 2835, 1571, 1461, 1389, 943 cm^{-1}. HRMS (ESI): Calcd for $C_{16}H_{35}N_2$ $[M+H]^+$ 255.2795, Found: 255.2778.

4.2.12. (1*R*,2*R*)-N^1,N^2-Bis(4-methylpentan-2-yl)cyclohexane-1,2-diamine dihydrochloride 1l·2HCl

According to the general procedure, **1l**·2HCl was obtained as a white solid. Yield: 47%. $[\alpha]_D^{25} = -69.8$ (*c* 0.5, H_2O). ^{1}H NMR (300 MHz, D_2O, 25 °C) δ: 0.88–0.97 (m, 12H, $CHCH_3$), 1.30–1.39 (m, 6H, NHCHCH_3), 1.43–1.61 (m, 2H, $CHCH_3$), 1.72–2.37 (m, 12H, $CHCH_2$ and CH_2 of DACH), 3.57–3.62 (m, 4H, NHCH). ^{13}C NMR (D_2O, 75 MHz) δ: 22.35, 23.09, 24.37, 24.71, 25.02, 25.59, 26.70, 26.81, 28.42, 28.57, 45.05, 45.10, 53.91, 53.99, 54.09, 54.17, 57.06, 57.43. IR: ν = 3427, 2958, 2871, 2694, 1590, 1471, 1391, 1043, 999 cm^{-1}. HRMS (ESI): Calcd for $C_{18}H_{39}N_2$ $[M+H]^+$ 283.3108, Found: 283.3117.

4.2.13. (1*R*,2*R*)-N^1,N^2-Bis(5-methylhexan-2-yl)cyclohexane-1,2-diamine dihydrochloride 1m·2HCl

According to the general procedure, **1m**·2HCl was obtained as a white solid. Yield: 81%. $[\alpha]_D^{25} = -70.6$ (*c* 0.52, H_2O). ^{1}H NMR (300 MHz, D_2O, 25 °C) δ: 0.88 (d, *J* = 6.5 Hz, 12H, $CHCH_3$), 1.24–1.38 (m, 6H, NHCHCH_3), 1.43–1.61 (m, 2H, $CHCH_3$), 1.65–2.30 (m, 16H, CH_2CH and CH_2 of DACH), 3.53 (s, 4H, NHCH). ^{13}C NMR (D_2O, 75 MHz) δ: 17.09, 19.32, 24.24, 24.33, 24.47, 24.66, 28.38, 28.58, 29.75, 29.89, 31.12, 31.24, 34.04, 34.09, 36.00, 36.30, 55.66, 55.69, 57.19, 57.43. IR: ν = 3404, 2954, 2869, 1589, 1468, 1389, 1064 cm^{-1}. HRMS (ESI): Calcd for $C_{20}H_{43}N_2$ $[M+H]^+$ 311.3421, Found: 311.3419.

4.2.14. (1*R*,2*R*)-N^1,N^2-Bis(3,5,5-trimethylhexyl)cyclohexane-1,2-diamine dihydrochloride 1n·2HCl

According to the general procedure, **1n**·2HCl was obtained as a white solid. Yield: 86%. $[\alpha]_D^{25} = -37.8$ (*c* 0.49, H_2O). ^{1}H NMR (300 MHz, D_2O, 25 °C) δ: 0.92 (d, 24H, $CHCH_3$ and $C(CH_3)_3$), 1.10–1.24 (m, 2H, $CHCH_3$), 1.40–2.29 (m, 16H, $CHCH_2$ and CH_2 of DACH), 3.05 (m, 2H, NHCH), 3.27–3.45 (m, 4H, $NHCH_2$). ^{13}C NMR (D_2O, 75 MHz) δ: 24.01, 24.25, 28.23, 29.36, 29.46, 31.77, 32.72, 37.23, 46.97, 52.59, 52.77, 59.80. IR: ν = 3406, 2954, 2867, 2703, 1587, 1465, 1393, 1364, 1015 cm^{-1}. HRMS (ESI): Calcd for $C_{24}H_{51}N_2$ $[M+H]^+$ 367.4047, Found: 367.4039.

4.3. General procedure for the catalytic Henry reaction

Ligand **1n** (0.6 mmol, 12 mol %) and $Cu(OAc)_2·H_2O$ (10 mg, 0.5 mmol, 10 mol %) were added with *i*-PrOH (1.0 mL) to a test tube, to give a deep blue solution after being slightly heated for 30 s and stirred for 1.0 h at 20 °C. Next, a solution of the corresponding aldehyde (0.5 mmol, 1.0 equiv) in *i*-PrOH (0.3 mL) was added, the reaction mixture was cooled to −20 °C, and stirred for 15 min. To the resulting solution was successively added nitroalkane (5.0 mmol, 10 equiv), and DIPEA (7.7 mol %, 5 mg), and the tube was put in a cooling circulation pump at the −20 °C. After 48 h, the mixture was purified by column chromatography on silica gel (30 g, PE/AcOEt, 4:1, v/v), to give the corresponding product. HPLC was used to determine the enantiomeric excess by Chiralpak IC, Chiracel OD-H, Chiralpak AD-H, or Chiralpak AS-H chiral columns.

(1S)-2-Nitro-1-phenylethanol ***3a****:* Chiralpak IC, *n*-hexane/*i*-PrOH, 90:10, 0.8 mL/min, λ = 220 nm, t_{minor} = 13.5 min, t_{major} = 14.4 min.

(1S)-1-Nitrobutan-2-ol ***3b****:* Chiralpak AD-H, *n*-hexane/*i*-PrOH, 90:10, 0.5 mL/min, λ = 210 nm, t_{minor} = 35.7 min, t_{major} = 54.1 min.

(1S)-1-Nitropentan-2-ol ***3c****:* Chiralpak AS-H, *n*-hexane/*i*-PrOH, 95:5, 0.8 mL/min, λ = 220 nm, t_{minor} = 35.2 min, t_{major} = 39.7 min.

(1S)-3-Methyl-1-nitrobutan-2-ol ***3d****:* Chiracel OD-H, *n*-hexane/*i*-PrOH, 98:2, 0.5 mL/min, λ = 210 nm, t_{minor} = 30.3 min, t_{major} = 34.7 min.

(1S)-1-Nitrohexan-2-ol ***3e****:* Chiracel OD-H, *n*-hexane/*i*-PrOH, 98:2, 0.5 mL/min, λ = 210 nm, t_{minor} = 41.4 min, t_{major} = 43.2 min.

(1S)-4-Methyl-1-nitropentan-2-ol ***3f****:* Chiralpak AD-H, *n*-hexane/*i*-PrOH, 95:5, 0.5 mL/min, λ = 210 nm, t_{minor} = 25.4 min, t_{major} = 36.2 min.

(1S)-3,3-Dimethyl-1-nitrobutan-2-ol ***3g****:* Chiralpak AD-H, *n*-hexane/*i*-PrOH, 95:5, 0.5 mL/min, λ = 210 nm, t_{minor} = 14.2 min, t_{major} = 14.6 min.

(1S)-1-Nitroheptan-2-ol ***3h****:* Chiralpak AD-H, *n*-hexane/*i*-PrOH, 95:5, 0.5 mL/min, λ = 210 nm, t_{minor} = 30.4 min, t_{major} = 43.7 min.

(1S)-1-Nitrooctan-2-ol ***3i****:* Chiralpak AD-H, *n*-hexane/*i*-PrOH, 95:5, 0.5 mL/min, λ = 210 nm, t_{minor} = 31.2 min, t_{major} = 47.1 min.

(1S)-1-Cyclohexyl-2-nitroethanol ***3j****:* Chiralpak AD-H, *n*-hexane/*i*-PrOH, 90:10, 1.0 mL/min, λ = 225 nm, t_{minor} = 8.7 min, t_{major} = 9.4 min.

(1S)-2-Nitro-1-(2-nitrophenyl)ethanol ***3k****:* Chiracel OD-H, *n*-hexane/*i*-PrOH, 90:10, 0.8 mL/min, λ = 215 nm, t_{minor} = 22.4 min, t_{major} = 25.1 min.

(1S)-2-Nitro-1-(3-nitrophenyl)ethanol ***3l****:* Chiracel OD-H, *n*-hexane/*i*-PrOH, 85:15, 0.5 mL/min, λ = 210 nm, t_{minor} = 36.6 min, t_{major} = 41.1 min.

(1S)-2-Nitro-1-(4-nitrophenyl)ethanol ***3m****:* Chiracel OD-H, *n*-hexane/*i*-PrOH, 80:20, 1.0 mL/min, λ = 225 nm, t_{minor} = 13.1 min, t_{major} = 16.2 min.

(1S)-1-(2-Chlorophenyl)-2-nitroethanol ***3n****:* Chiracel OD-H, *n*-hexane/*i*-PrOH, 97:3, 0.5 mL/min, λ = 210 nm, t_{minor} = 45.6 min, t_{major} = 47.4 min.

(1S)-1-(3-Chlorophenyl)-2-nitroethanol ***3o****:* Chiracel OD-H, *n*-hexane/*i*-PrOH, 90:10, 1.0 mL/min, λ = 225 nm, t_{minor} = 20.6 min, t_{major} = 25.7 min.

(1S)-1-(4-Chlorophenyl)-2-nitroethanol ***3p****:* Chiralpak AD-H, *n*-hexane/*i*-PrOH, 85:15, 0.8 mL/min, λ = 215 nm, t_{minor} = 13.3 min, t_{major} = 16.9 min.

(1S)-1-(2-Methoxyphenyl)-2-nitroethanol ***3q****:* Chiracel OD-H, *n*-hexane/*i*-PrOH, 90:10, 0.8 mL/min, λ = 215 nm, t_{minor} = 15.7 min, t_{major} = 18.9 min.

(1S)-1-(3-Methoxyphenyl)-2-nitroethanol ***3r****:* Chiracel OD-H, *n*-hexane/*i*-PrOH, 70:30, 0.6 mL/min, λ = 214 nm, t_{minor} = 15.2 min, t_{major} = 18.8 min.

(1S)-2-Nitro-1-p-tolylethanol ***3s****:* Chiracel OD-H, *n*-hexane/*i*-PrOH, 90:10, 1.0 mL/min, λ = 215 nm, t_{minor} = 11.2 min, t_{major} = 14.9 min.

(1S)-1-(4-Fluorophenyl)-2-nitroethanol ***3t****:* Chiralpak AD-H, *n*-hexane/*i*-PrOH, 90:10, 0.8 mL/min, λ = 215 nm, t_{minor} = 21.9 min, t_{major} = 22.8 min.

(1S)-1-Biphenyl-4-yl-2-nitroethanol ***3u****:* Chiracel OD-H, *n*-hexane/*i*-PrOH, 85:15, 0.8 mL/min, λ = 215 nm, t_{minor} = 20.6 min, t_{major} = 24.9 min.

(2S,3E)-1-Nitro-4-phenylbut-3-en-2-ol ***3v****:* Chiracel OD-H, *n*-hexane/*i*-PrOH, 85:15, 1.0 mL/min, λ = 206 nm, t_{minor} = 20.1 min, t_{major} = 29.8 min.

(1R)-1-(2-Furyl)-2-nitroethanol ***3w****:* Chiralpak AD-H, *n*-hexane/*i*-PrOH, 95:5, 1.0 mL/min, λ = 225 nm, t_{minor} = 26.1 min, t_{major} = 27.8 min.

(1S)-1-(1-Naphthyl)-2-nitroethanol ***3x****:* Chiracel OD-H, *n*-hexane/*i*-PrOH, 85:15, 0.8 mL/min, λ = 215 nm, t_{minor} = 17.7 min, t_{major} = 26.0 min.

(1S)-1-(2-Naphthyl)-2-nitroethanol ***3y****:* Chiracel OD-H, *n*-hexane/*i*-PrOH, 80:20, 1.0 mL/min, λ = 225 nm, t_{minor} = 25.9 min, t_{major} = 36.0 min.

(S)-1-(4-(tert-Butyldimethylsilyloxy)phenyl)-2-nitroethanol ***5****:* Chiracel OD-H, *n*-hexane/*i*-PrOH, 90:10, 1.0 mL/min, λ = 254 nm, t_{minor} = 7.21 min, t_{major} = 8.88 min.

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