Full Paper

Applied Organometallic Chemistry

Received: 13 September 2013 Revised: 23 October 2013 Accepted: 6 November 2013 Published online in Wiley Online Library: 30 January 2014

(wileyonlinelibrary.com) DOI 10.1002/aoc.3107

Asymmetric Henry reactions of aldehydes with various nitroalkanes catalyzed by copper(II) complexes of novel chiral *N*-monoalkyl cyclohexane-1,2-diamines

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A number of novel chiral diamines 3, (1*R*,2*R*)-*N*-monoalkylcyclohexane-1,2-diamines, were designed and synthesized from *trans*-cyclohexane-1,2-diamine and applied to the catalytic asymmetric Henry reaction of benzaldehyde and nitromethane to provide β-nitroalcohol in high yield (up to 99%) and good enantiomeric excess (up to 89%). By using ligand (1*R*,2*R*)-*N*[1]-(4-methylpentan-2-yl)cyclohexane-1,2-diamine (3g), the reaction was optimized in terms of the metal ion, temperature, solvent and base. Further experiments indicated that the complex, 3g–Cu(OAc)$_2$, was an efficient catalyst in the asymmetric Henry reaction between different aldehydes and nitromethane, and the desired products have been obtained with high chemical yields (up to 99%) and high enantiomeric excess (up to 93%). The optimized catalyst promoted the diastereoselective Henry reaction of various aldehyde substrates and nitroalkane, which gave the corresponding *anti*-selective adduct with up to 99% yield and 83:17 *anti*/*syn* selectivity. Upon scaling up to gram quantities, the β-nitroalcohol was obtained in good yield (96%) with excellent selectivities (93% *ee*). The chiral induction mechanism was tentatively explained on the basis of a previously proposed transition-state model. Copyright © 2014 John Wiley & Sons, Ltd.

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Keywords: asymmetric catalysis; Henry reaction; copper; *N*-monoalkyl (1*R*,2*R*)-diaminocyclohexane; β-nitroalcohol

Introduction

The Henry reaction is one of the most important methods for the formation of C—C bond in organic chemistry[1] and the resulting products, chiral β-nitroalcohols, are important intermediates and can be further transformed into other useful derivatives such as carboxylic acids and amino alcohols in the synthesis of relevant biologically active compounds.[2–4] The first asymmetric version of the Henry reaction was reported by Shibasaki in 1992.[5] Since then, interest in this area has been expanded upon considerably and various catalyst systems for this reaction have been developed (e.g. rare earth metal BINOL complexes,[6] Cu-bis(oxazoline) (BOX) complexes,[7–9] dinuclear Zn complexes[4] and Zn salts-chiral amino alcohol).[10]

In recent years, metal–salen complexes, especially the C_2-symmetric metallosalen compounds (see Fig. 1, ligand **1**), have been proved to be useful catalysts for a wide range of organic reactions.[11–14] Copper(II) complexes of chiral secondary diamines derived from (1*R*,2*R*)-1,2-diaminocyclohexane (DACH) (see Fig. 1, ligand **2**) were first successfully applied for the asymmetric Henry reaction with enantioselectivity up to 94% by Skarżewski and his co-workers.[15] Asymmetric induction of asymmetric Henry reaction is imparted from copper(II) complexes and it begins with the statement of the impact of the Jahn-Teller effect on Cu(II) coordination.[8] 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.[15] Subsequently, more secondary diamine–copper complexes with bulky aromatic substituents[16–23] (e.g. **2a**,[16] Fig. 2) in macrocyclic units[24–28] (e.g. **2b**,[28] Fig. 2) or with a nitrogen-containing heterocyclic ring[29,30] (e.g. **2c**,[30] Fig. 2) were synthesized and applied in Cu-catalyzed asymmetric Henry reactions, which afforded various β-nitroalcohols in excellent yield and enantioselectivities under the optimized reaction conditions. Other more specific diamines, such as secondary amine–tertiary amines[31,32] (e.g. **2d**,[31] Fig. 2) and tertiary amine–

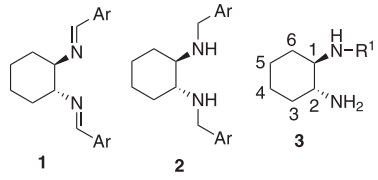

Figure 1. Chiral diamine or diimine ligands derived from (1*R*,2*R*)-diaminocyclohexane: C_2-symmetric salen ligand (**1**), secondary diamine ligand (**2**), *N*-monoalkyl diamine ligand (**3**). R^1 is an alkyl group.

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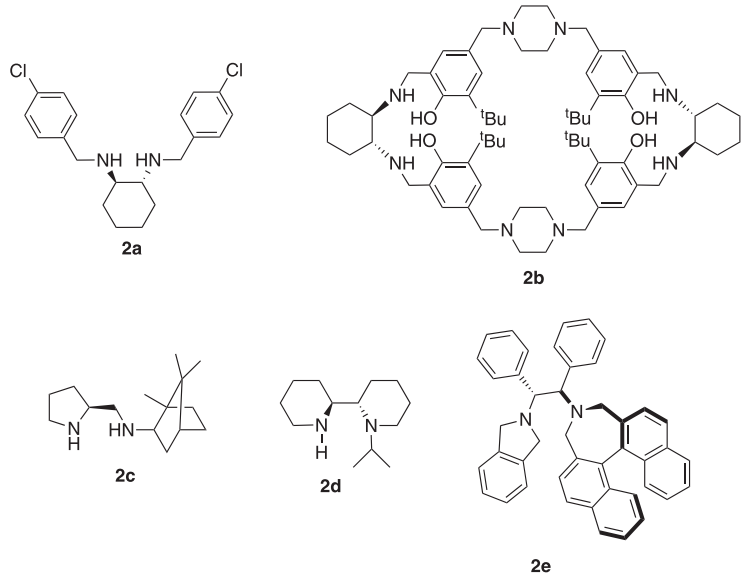


Figure 2. Chiral diamine ligands used in asymmetric Henry reaction.

tertiary amines[33–35] (e.g. **2e**,[34] Fig. 2), were prepared and applied to asymmetric Henry reactions, and Henry adducts were produced in high yield with excellent enantiomeric excess. Despite significant progress in this field, there are still some shortcomings for this kind of reaction, such as rather complicated ligand structures (some ligands are difficult to synthesize or the yield is low) in addition to substrate specificity limitations.

Before long, Zhu *et al*. reported that a diimine (**1a**, Fig. 3) catalyst in the asymmetric Michael reaction of 4-hydroxycoumarins and 2-cyclohexen-1-one was formed *in situ* with a primary amine–imine (**4**, Fig. 3) system.[36] Their results hint that this may occur in an analogous addition reaction. In other words, C_2-symmetric salen diimine or secondary diamine systems are not essential for the catalyst, and primary amine–imine or primary amine–secondary amine may be catalytically efficient in the similar asymmetric reaction. The surmise leads us to design a very simple and novel chiral diamine ligand for the analogous addition reaction. To our delight, it is reported that some primary amine–imine[37] (Fig. 4, **5a**), primary amine–tertiary amines[38,39] (Fig. 4, **5b** and **5c**) were recently applied to the catalytic asymmetric Henry reaction of benzaldehyde and nitromethane to provide β-nitroalcohol at low enantiomeric excess values (Fig. 4; *ee* 29%, 19%, 36%). This confirmed that such simple ligands have certain catalytic activities in the asymmetric Henry reaction. Therefore, we believe that some simple ligands that are easy to synthesize could be gained with a rational design for the asymmetric Henry reaction.

In our recent study, we have designed and developed a series of *N*-monoalkyl derivatives of DACH (see Fig. 1, ligand **3**), which can be expected as chiral ligands for asymmetric catalysis in addition to the preparation of Pt(II) complexes for antitumor agent screening.[40] Thus this kind of simple and novel ligand (primary amine–secondary amines) with copper(II) ions has been investigated herein as catalysts in the asymmetric Henry reaction. Here, we report that a series of Cu(II) complexes based on the novel ligands show excellent catalytic activity in terms of activity and selectivity. By using ligand **3**, we would like to prove that those ligands, including only one simple alkyl group, can also play a similar role to aromatic groups in the asymmetric Henry reaction with copper(II) ions in an excellent catalytic effect.

Results and Discussion

Synthesis of Chiral Ligands

The synthetic process for novel chiral ligands **3** (*N*-monoalkyl diamines) was described by our group previously[40] (as shown in Scheme 1). The *N*-monoalkyl diamines were developed by protecting one of amino groups with $(Boc)_2O$ first, followed by Schiff base condensation with aldehyde or ketone and *in situ* reduction using $NaBH_4$. In this way, a number of such compounds (**3a–3o**) were obtained in their hydrochloride salts in a yield of 42–84%.

The Asymmetric Henry Reaction

Ligand **3** was first examined in the Henry reaction between benzaldehyde and nitromethane. An optimized method reported in the literature[16] was adopted and developed to screen the ligands that can form efficient catalysts with Cu(II) ions in the Henry reaction. The Henry reactions were performed on a 0.5 mmol scale, using 12 mol% of respective diamine, 10 mol% $Cu(OAc)_2.H_2O$, 10 equiv. nitromethane and 7.7 mol% *i*-Pr_2NEt in *i*-PrOH at −20°C for 24 h (−30°C, 70 h).[16] The results showed that under these conditions the desired product (**6a**) was obtained in good yield with enantiomeric excess in most cases, as summarized in Table 1. The ligands with *N*-alkyl groups usually gave products with up to 89% *ee* (the (*S*)-enantiomer is the major product). Among them, those with relatively long alkyl chains, such as **3f**, **3g**, **3k**, **3m** and **3o**, afforded reasonable results

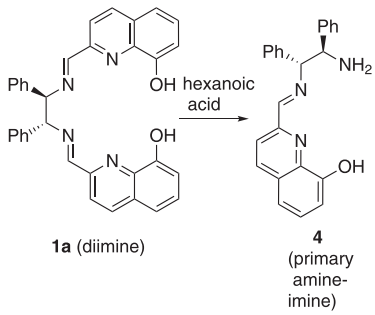


Figure 3. Reported chiral ligand derived from the *in situ* preparation of primary amine–imine.

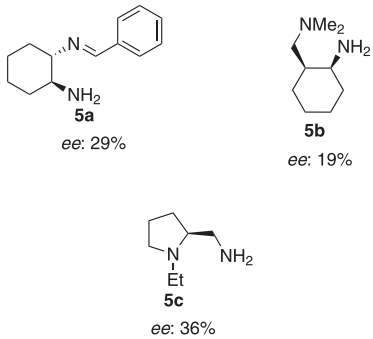
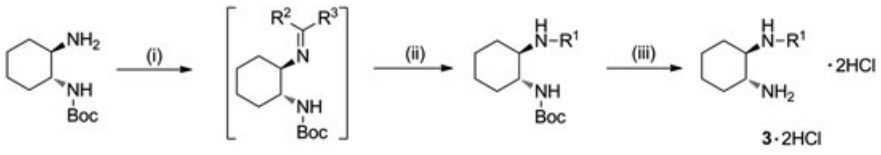


Figure 4. Chiral diamine ligands: primary amine–imine and primary amine–tertiary amine (*ee*: the asymmetric Henry reaction of benzaldehyde with nitromethane catalyzed by copper(II) complexes).



Scheme 1. Synthesis of chiral ligand **3**.2HCl: (i) aldehyde or ketone, MeOH; (ii) $NaBH_4$; (iii) HCl/EtOAc, 0°C.

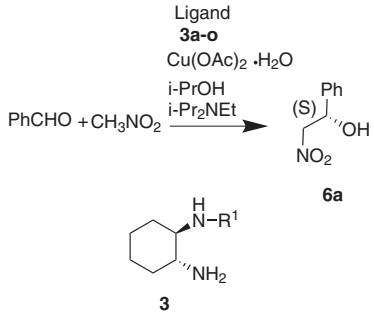
(≥88% *ee*; Table 1, entries 6, 7, 11, 13 and 15), while those such as **3c** and **3h** gave poor results with only 45% and −6% *ee* (the (*R*)-enantiomer is the major product), respectively (Table 1, entries 3 and 8; **3h** gave a reverse enantioselectivity). The best results were obtained by using ligands **3g**, **3k** and **3o** with 89% *ee* (Table 1, entries 7, 11 and 15). Based upon the yield, **3g** was the best ligand for the Henry reaction (up to 99%).

It is notable that ligands with a methyl group next to the CH—N bond usually gave a good enantiomeric excess (Table 1, entries 1, 4, 7, 11, 13 and 15, at least 82% *ee*) and the results improved along with the increase of carbon atom numbers in the alkyl carbon chain. However, ligand **3h** with three methyl groups did not afford good results, which appeared to show that bulky substituted groups on the nitrogen atom are not necessary.

By using the best ligand, **3g**, reaction conditions such as the metal, temperature, solvent and base were examined in the Henry reaction of benzaldehyde and nitromethane (Table 2). When the reaction was carried out without a catalyst, no reaction took place (entry 1). When reactions were performed in the absence of base (*i*-Pr_2NEt, entry 2) or chiral ligand **3g** (entry 3), nitroalcohols were produced with 96% and 60% yield, respectively, but, unfortunately, as a racemic compound or with the desired product in very low enantiomeric excess (6%). Very low enantioselective reaction proceeded in the presence of 12 mol% **3g** and 7.7 mol% *i*-Pr_2NEt to give **6a** in very low yield (6%) and 2% *ee* (entry 4). Benzaldehyde could react smoothly with nitromethane in the presence of 12 mol% **3g**, 10 mol% $Cu(OAc)_2.H_2O$, 10 equiv. CH_3NO_2 and 7.7 mol% base at −20°C for 24 h in 99% yield and 89% *ee* (entry 6). Then various copper salts were evaluated in combination with **3g** and *i*-Pr_2NEt. As a consequence, several divalent copper salts were effective for the asymmetric Henry reaction, and $Cu(OAc)_2$ gave the best value of 89% *ee* (entry 6). Other metal (acetate) complexes were also tested as catalysts for the reaction. The application of ligand **3g** in combination with $Co(OAc)_2$ did not affect the yield but led to significant loss in enantioselectivity (entry 10), while with $Zn(OAc)_2$ and **3g** as the catalyst only 12% yield and 3% *ee* of **6a** were obtained (entry 11). Reducing the temperature to −40°C increased the value to 90% *ee* (entry 13). A further decrease to −60°C did not have a significant effect on enantiomeric excess, but led to very low yield (entry 14). Thus −40° was found to be the optimum temperature. The reaction was further subjected to solvent variation (entries 13, 15–17). It was demonstrated that the solvent affected to a limited extent the yield and enantioselectivity. With *i*-PrOH as the solvent (entry 13), the nitroalcohol was isolated in 90% *ee*. A series of bases were also tested for the Henry reaction of benzaldehyde with nitromethane (entries 18–20). Et_3N turned out to be the best choice, with 91% *ee* and 99% yield (entry 18), while *i*-Pr_2NEt induced almost the same result (entry 13). The amount of base (Et_3N) additive had little influence on the enantioselectivity but was responsible for the yield (entries 18, 21,22). While the base loading decreased to 2.6 mol%, the reaction could go to completion within 72 h in 72% yield with 91% *ee* (entry 21). An increase of the Et_3N loading from 7.7 to 15.4 mol% gave a minute reduction in enantioselectivity (90%, entry 22). This indicates that our catalytic system can tolerate a broad range of quantities of base additive, and the uncoordinated base-promoted background reaction is negligible. Based on yield and the enantioselectivity of products, the optimization of reaction conditions was obtained as follows: reactions were performed on a 0.5 mmol scale, with 12 mol% ligand, 10 mol% $Cu(OAc)_2.H_2O$, 10 equiv. CH_3NO_2 and 7.7 mol% Et_3N in *i*-PrOH at −40°C for 24 h (entry 18).

On the basis of the optimized reaction parameters, the scope of various aldehydes was explored (Table 3: aromatic aldehydes, entries 1–13; aliphatic aldehydes, entries 14–16). A variety of aromatic aldehydes provided the corresponding β-nitroalcohols with moderate to high yields (up to 99%) and enantioselectivities ranging from 77% to 93% (**6o** gave a reverse enantioselectivity, −77%; the (*R*)-enantiomer is the

Table 1. Screening *N*-monoalkyl diamine ligands in the Henry reaction of benzaldehyde and nitromethane



Entry[a]	Ligand	R^1	Yield (%)[b]	*ee* (%)[c]
1	**3a**	*i*-Pr	96	85[d]
2	**3b**	*n*-Bu	89	73
3	**3c**	*i*-Bu	90	45
4	**3d**	*s*-Bu	90	82
5	**3e**	*n*-Pentyl	99	74
6	**3f**	1-Ethylpropyl	99	88
7	**3g**	1,3-Dimethylbutyl	99	89
8[e]	**3h**	Neopentyl	90	−6
9	**3i**	Cyclopentyl	90	75
10	**3j**	*n*-Hexyl	99	72
11	**3k**	2-Hexyl	95	89
12	**3l**	Cyclohexyl	95	79
13	**3m**	2-Heptyl	99	88
14	**3n**	3-Octyl	90	82
15	**3o**	2-Undecyl	96	89

[a]Reactions were performed on a 0.5 mmol scale, with 12 mol% of respective *N*-monoalkyl diamine **3a–o**, 10 mol% of $Cu(OAc)_2.H_2O$, 10 equiv. CH_3NO_2 and 7.7 mol% of *i*-Pr_2NEt in *i*-PrOH at −20°C for 24 h.

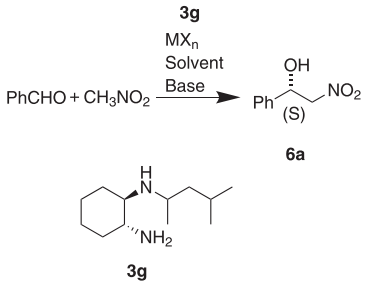
[b]Yield of isolated product.

[c]Enantiomeric excess was determined by HPLC using Chiralpak IC column (see Supporting Information).

[d]The (*S*)-enantiomer was the major product.

[e]The (*R*)-enantiomer was the major product.

Table 2. Optimization of reaction conditions for the Henry reaction of benzaldehyde and nitromethane with ligand **3g**



Entry[a]	Ligand	MX_n	Base	Solvent	*T* (°C)	Yield (%)[b]	*ee* (%)[c]
1	—	—	—	*i*-PrOH	−20	—	—
2	—	—	*i*-Pr_2NEt	*i*-PrOH	−20	96	0
3	**3g**	—	—	*i*-PrOH	−20	60	6
4	**3g**	—	*i*-Pr_2NEt	*i*-PrOH	−20	4	2
5[d]	**3g**	$Cu(OAc)_2.H_2O$	—	*i*-PrOH	−20	84	89
6[e]	**3g**	$Cu(OAc)_2.H_2O$	*i*-Pr_2NEt	*i*-PrOH	−20	99	89
7	**3g**	$CuCl_2$	*i*-Pr_2NEt	*i*-PrOH	−20	99	85
8	**3g**	$Cu(NO_3)_2.3H_2O$	*i*-Pr_2NEt	*i*-PrOH	−20	15	60
9	**3g**	CuBr	*i*-Pr_2NEt	*i*-PrOH	−20	86	74
10	**3g**	$Co(OAc)_2.4H_2O$	*i*-Pr_2NEt	*i*-PrOH	−20	99	3
11	**3g**	$Zn(OAc)_2.2H_2O$	*i*-Pr_2NEt	*i*-PrOH	−20	12	3
12	**3g**	$Cu(OAc)_2.H_2O$	*i*-Pr_2NEt	*i*-PrOH	0	99	81
13	**3g**	$Cu(OAc)_2.H_2O$	*i*-Pr_2NEt	*i*-PrOH	−40	99	90
14[f]	**3g**	$Cu(OAc)_2.H_2O$	*i*-Pr_2NEt	*i*-PrOH	−60	10	92
15	**3g**	$Cu(OAc)_2.H_2O$	*i*-Pr_2NEt	EtOH	−40	99	88
16	**3g**	$Cu(OAc)_2.H_2O$	*i*-Pr_2NEt	CH_2Cl_2	−40	99	82
17	**3g**	$Cu(OAc)_2.H_2O$	*i*-Pr_2NEt	THF	−40	67	86
18	**3g**	$Cu(OAc)_2.H_2O$	Et_3N	*i*-PrOH	−40	99	91
19	**3g**	$Cu(OAc)_2.H_2O$	Pyridine	*i*-PrOH	−40	43	88
20	**3g**	$Cu(OAc)_2.H_2O$	Cs_2CO_3	*i*-PrOH	−40	95	66
21[g]	**3g**	$Cu(OAc)_2.H_2O$	Et_3N	*i*-PrOH	−40	71	91
22[h]	**3g**	$Cu(OAc)_2.H_2O$	Et_3N	*i*-PrOH	−40	83	90

[a]General procedure: reactions were performed on a 0.5 mmol scale (0.3 ml corresponding solvent), with 12 mol% **3g** (1 ml corresponding solvent), 10 mol% MX_n, 10 equiv. CH_3NO_2 and 7.7 mol% base (0.2 ml corresponding solvent) at corresponding temperature for 24 h.

[b]Yield of isolated product.

[c]Enantiomeric excess was determined by HPLC using Chiralpak IC chiral column.

[d]Reaction was performed for 72 h.

[e]See Table 1, entry 7.

[f]Reaction was performed for 72 h.

[g]The amount of Et_3N was 2.6 mol% (1.7 mg, 0.2 ml) and the reaction was performed for 72 h.

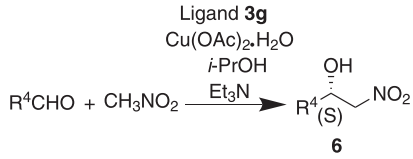
[h]The amount of Et_3N was 15.4 mol% (10.0 mg, 0.2 ml).

major product, entry 13). It is noted that the electronic character of the substituent on the aromatic ring and its steric hindrance have a slight influence on the enantioselectivity of the resulting products. In general, no matter whether the aromatic aldehydes were electron rich (entries 1–4), electron poor (entries 5–8), sterically hindered (entries 9–11) or heterocyclic (entry 12), all of them smoothly underwent the Henry reaction with high yields (up to 99%) and good enantioselectivities (up to 93%). The highest value of 93% *ee* accompanied by 97% yield was found for 2-methoxybenzaldehyde (entry 1). However, for aliphatic aldehydes, the corresponding β-nitroalcohols were obtained with relatively low yields (38–53%) and enantioselectivities (75–86%). It was noted that the reaction activity of the aliphatic aldehyde was relatively low (low yields), but the enantioselectivity of products was not affected (moderate to good selectivity). These results demonstrated that **3g** can be effectively applied in the Henry reaction with various aromatic aldehydes.

Subsequently, in view of the less explored nitroalkane substrate scope, nitroethane and 1-nitropropane were tested in the diastereoselective Henry reaction (Table 4). The reaction of aromatic aldehydes gave the respective β-nitroalcohols with good to high yields (up to 99%), good enantioselectivities (up to 90%) and moderate diastereoselectivities (*dr*, *anti*:*syn*, up to 83:17, favoring the *anti* product; Table 4, entries 1–11). For the aliphatic aldehyde, the reaction activity is relatively low and the major products are the *syn* isomers (Table 4, entries 12 and 13).

Upon scaling up to gram quantities (benzaldehyde, 10 mmol, 1.06 g), the desired product **6a** was obtained in high yield (96%)

Table 3. Henry reactions of different aromatic aldehydes (R^4CHO) and nitromethane catalyzed by **3g**–$Cu(OAc)_2$



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Entry[a]	R^4	**6**	Yield (%)[b]	*ee* (%)[c]
1	2-$MeOC_6H_4$	**6b**	97	93[d]
2	3-$MeOC_6H_4$	**6c**	91	92
3	4-$MeOC_6H_4$	**6d**	98	92
4	4-MeC_6H_4	**6e**	90	91
5	2-$NO_2C_6H_4$	**6f**	90	80
6	4-FC_6H_4	**6h**	97	87
7	3-ClC_6H_4	**6i**	99	91
8	4-ClC_6H_4	**6j**	92	90
9	4-PhC_6H_4	**6k**	90	92
10	1-Naphthyl	**6l**	93	91
11	2-Naphthyl	**6m**	96	91
12	2-Furyl	**6n**	99	87
13	PhCH=CH-	**6o**	89	−77[e]
14	*i*-Pr	**6p**	53	86
15	*n*-Bu	**6q**	29	82
16	Cyclohexyl	**6r**	38	75

[a]Reactions were performed on a 0.5 mmol scale (0.3 ml *i*-PrOH), with 12 mol% **3g** (1 ml *i*-PrOH), 10 mol% $Cu(OAc)_2.H_2O$, 10 equiv. CH_3NO_2, 7.7 mol% Et_3N (3.9 mg, 0.2 ml *i*-PrOH) in *i*-PrOH at −40°C for 24 h.

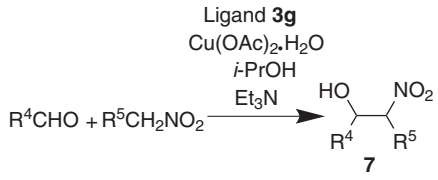
[b]Yield of isolated product.

[c]Enantiomeric excess was determined by HPLC using chiral column (see Supporting Information).

[d]The (*S*)-enantiomer was the major product.

[e]The (*R*)-enantiomer was the major product.

Table 4. Henry reactions of different aldehydes (R^4CHO) and nitroalkanes ($R^5CH_2NO_2$) catalyzed by **3g**–$Cu(OAc)_2$



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Entry[a]	R^5	R^6	**7**	Yield (%)[b]	*dr* (*anti*:*syn*)[c]	*ee* (%)[d]
1	Ph	Me	**7a**	99	78:22	87/85
2	Ph	Et	**7b**	88	74:26	89/87
3	2-$NO_2C_6H_4$	Me	**7c**	86	76:24	86/72
4	3-$NO_2C_6H_4$	Me	**7d**	97	78:22	85/66
5	4-$NO_2C_6H_4$	Me	**7e**	87	71:29	–/49
6	4-$NO_2C_6H_4$	Et	**7f**	86	66:34	78/58
7	2-$MeOC_6H_4$	Me	**7g**	84	83:17	84/90
8	3-$MeOC_6H_4$	Me	**7h**	85	78:22	87/88
9	4-ClC_6H_4	Me	**7i**	83	77:23	85/80
10	4-ClC_6H_4	Et	**7j**	86	79:21	86/83
11	4-$CH_3C_6H_4$	Et	**7k**	91	72:28	85/88
12	*i*-Pr	Me	**7l**	34	22:78	51/85
13	Cyclohexyl	Me	**7m**	30	37:63	12/56

[a]Reactions were performed on a 0.5 mmol scale (0.3 ml *i*-PrOH), with 12 mol% **3g** (1 ml *i*-PrOH), 10 mol% $Cu(OAc)_2.H_2O$, 10 equiv. CH_3NO_2 and 7.7 mol% Et_3N (3.9 mg, 0.2 ml *i*-PrOH) in *i*-PrOH at −40°C for 24 h.

[b]Yield of isolated product.

[c]Diastereomeric ratios were determined by HPLC using Chiracel chiral column (see Supporting Information).

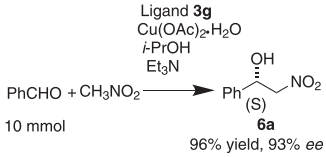
[d]Diastereomeric ratios and enantiomeric excess were determined by HPLC using Chiracel chiral column.

with excellent selectivity (93% *ee*) using 12 mol% **3g** (20 ml *i*-PrOH), 10 mol% $Cu(OAc)_2.H_2O$ at −40°C (Scheme 2). Therefore **3g**–$Cu(OAc)_2$ could be used as a suitable catalyst to prepare large amounts of β-nitroalcohol with high enantiomeric excess value.

Based on the generally accepted model proposed by Evans,[8] Kureshy[28] and Kodama,[39] a general mechanism for the asymmetric Henry reaction is herein proposed (Fig. 5). The copper(II) ion with an octahedral geometry has four strong coordination sites at the equatorial positions and two weak coordination sites at the apical positions due to the Jahn–Teller effect. Two nitrogen atoms of ligand **3g** occupy two neighboring coordination sites. Both the aldehyde and nitromethane are efficiently activated by coordination to the equatorial and the apical position of the metal atom, respectively. To reduce spatial hindrance, the *Re* face of the carbonyl group of benzaldehyde is much more accessible to a nucleophilic group (nitromethane) than the *Si* face (A). Furthermore, the attacking group will strongly increase repulsion between phenyl subunits as in transition state B.

Conclusion

A number of chiral *N*-monoalkyl cyclohexane-1,2-diamines (ligand **3**) have been designed and applied to form the corresponding copper(II) complexes as catalysts in the asymmetric Henry reaction of various aldehydes and nitromethane. The results showed that most catalysts consisting of **3g**–$Cu(OAc)_2$ have brought about good yields and enantiomeric excess for the desired product. Further investigation on the copper(II) complex, **3g**–$Cu(OAc)_2$, indicated that it is an efficient catalyst in the asymmetric Henry reaction between various aldehydes and nitromethane. The resulting β-hydroxy nitroalkanes have been obtained with high chemical yields (up to 99%) and high enantiomeric excess (up to 93%). The optimized catalyst promoted the diastereoselective Henry reaction of various aldehyde substrates and nitroalkane, and gave the corresponding *anti*-selective adduct with up to a 99% yield and 83:17 *anti*/*syn* selectivity. Our results show that **3g**–$Cu(OAc)_2$ can be applied in the asymmetric Henry reaction to obtain large amounts of β-nitroalcohol with high enantioselectivity.



Scheme 2. Scale-up experiments. Reaction conditions: reactions were performed at a 10 mmol scale (6 ml *i*-PrOH), 12 mol% **3g** (20 ml *i*-PrOH), 10 mol% $Cu(OAc)_2.H_2O$, 10 equiv. CH_3NO_2, 7.7 mol% Et_3N (78 mg, 4 ml *i*-PrOH) at −40°C for 24 h.

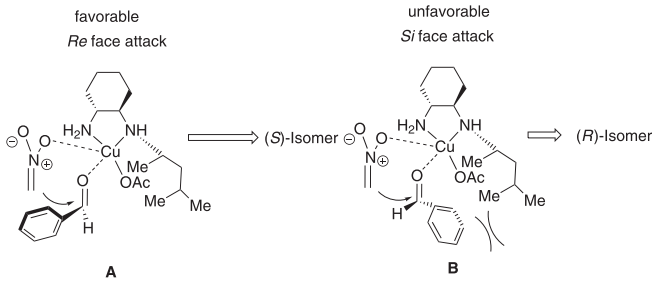


Figure 5. Proposed transition state for the catalytic asymmetric Henry reaction with **3g** as the ligand.

Experimental

General

All chemicals and solvents were of analytical reagent grade and used without further purification. $(Boc)_2O$ and (1*R*,2*R*)-DACH were obtained from a local chemical company. IR spectra were measured on KBr pellets on a Nicolet IR200 FT-IR spectrometer in the range 4000–400 cm^{-1}, and ^1H NMR and ^{13}C NMR spectra were recorded with a Bruker 300 MHz or 500 MHz spectrometer. Elemental analyses for C, H and N were done on a Vario MICRO CHNOS Elementar elemental analyzer. Mass spectra were measured on an Agilent accurate mass 6224 TOF LC-MS system.

Synthesis of Ligand 3

The corresponding aldehyde or ketone (80 mmol) was added to the stirring solution of mono-Boc protected (1*R*,2*R*)-DACH (40 mmol) in MeOH (150 ml). After the mixture was kept for 2 h at room temperature, it was cooled in an ice-water bath, followed by adding $NaBH_4$ (120 mmol) slowly, and kept stirred overnight at 50°C. Water (10 ml) was then added to the above mixture and white solids were obtained by concentrating the solution. After addition of 50 ml water, the aqueous phase was extracted with EtOAc (50 ml × 3). The combined organic extracts were washed with saturated NaCl solution and dried with anhydrous Na_2SO_4. By concentrating the solution *in vacuo*, the intermediate N^1-monoalkyl, N^2-Boc-(1*R*,2*R*)-diaminocyclohexane was obtained. The intermediate was then dissolved in absolute ether (75 ml) and a solution of HCl–EtOAc (1 mol l^{-1}, 50 ml) was added slowly with stirring. The mixture was kept stirred for 12 h at room temperature. The white solid was filtered off, washed with absolute ether and dried *in vacuo*. The product was obtained as dihydrochloride salt (**3**.2HCl) (see Supporting Information, ^1H and ^{13}C NMR spectra of ligand **3**). Since a new stereogenic center was generated when a branched alkyl group was linked to one of the nitrogen atoms of (1*R*,2*R*)-cylcohexyldiamine, such as ligands **3d**, **3g**, **3k**, **3m**, **3n** and **3o**, the ligands used were a mixture of diastereomers.

(1*R*,2*R*)-N^1-Isopropylcyclohexane-1,2-diamine dihydrochloride (**3a**.2HCl)

White powder; yield 7.33 g, 80%; $[\alpha]_D^{25} = -45.2$ (c 0.90, H_2O); IR (KBr) $\upsilon = 3431$, 2975, 2812, 1585, 1450, 1032 cm^{-1}; ^1H NMR (300 MHz, D_2O, 25°C): $\delta = 1.33$ (d, 6H, $J = 6.5$ Hz, $CH(CH_3)_2$), 1.38–2.32 (m, 8H, CH_2 of DACH), 3.38–3.48 (m, 2H, NHC*H* and NH_2CH), 3.64–3.73 (m, 1H, $NHCH(CH_3)_2$); ^{13}C NMR (75 MHz, D_2O, 25°C) $\delta = 19.5$ (C4), 22.0 (C5), 25.0 (2C, CH_3), 28.8 (C6), 32.0 (C3), 51.5 (CH), 54.4 (C1), 58.1 (C2); HRMS (ESI) calcd for $C_9H_{21}N_2$ $[M+H]^+$ 157.1705, found 157.1693. Anal. Calcd (%) for $C_9H_{22}Cl_2N_2$: C, 47.16; H, 9.68; N, 12.22. Found: C, 47.22; H, 9.69; N, 12.23.

(1*R*,2*R*)-N^1-*n*-Butylcyclohexane-1,2-diamine dihydrochloride (**3b**.2HCl)

White powder; yield 6.81 g, 70%; $[\alpha]_D^{25} = -43.0$ (c 0.44, H_2O); IR (KBr) $\upsilon = 3416$, 2942, 2870, 1607, 1519, 1458, 1027 cm^{-1}; ^1H NMR (300 MHz, D_2O, 25°C) $\delta = 0.93$ (t, 3H, $J = 7.4$ Hz, CH_2CH_3), 1.38–1.40 (m, 4H, $NHCH_2CH_2CH_2CH_3$), 1.51–2.32 (m, 8H, CH_2 of DACH), 3.04–3.27 (m, 2H, $NHCH_2$), 3.40–3.50 (m, 2H, NHC*H* and NH_2CH); ^{13}C NMR (75 MHz, D_2O, 25°C) $\delta = 15.0$ (CH_3), 21.4 (CH_3CH_2), 24.6 (C4), 24.7 (C5), 28.3 (C6), 29.9 (C3), 31.6 ($CH_3CH_2CH_2$), 47.5 ($NHCH_2$), 53.5 (C2), 60.6 (C1); HRMS (ESI) calcd for $C_{10}H_{23}N_2$ $[M+H]^+$ 171.1861, found 171.1852. Anal. Calcd (%) for $C_{10}H_{24}Cl_2N_2$: C, 49.38; H, 9.95; N, 11.52. Found: C, 49.30; H, 9.92; N, 11.46.

(1*R*,2*R*)-N^1-Isobutylcyclohexane-1,2-diamine dihydrochloride (**3c**.2HCl)

White powder; yield 7.10 g, 73%; $[\alpha]_D^{25} = -33.0$ (c 0.52, H_2O); IR (KBr) $\upsilon = 3430$, 2945, 2871, 1615, 1519, 1470, 1456, 1027 $cm^{-}1$; ^1H NMR (300 MHz, D_2O, 25°C) $\delta = 1.00$ (d, 6H, $J = 6.7$ Hz, $CH(CH_3)_2$), 1.32–1.84 (m, 6H, CH_2 of DACH), 2.02–2.11 (m, 1H, $CH(CH_3)_2$), 2.16–2.33 (m, 2H, CH_2 of DACH), 2.93–3.11 (m, 2H, $NHCH_2CH$), 3.35–3.55 (m, 2H, NHC*H* and NH_2CH); ^{13}C NMR (75 MHz, D_2O, 25°C) $\delta = 21.7$ ($CHCH_3$), 22.0 ($CHCH_3$), 25.1 (C4), 25.2 (C5), 28.5 (C6), 28.7 (CH), 32.2 (C3), 53.9 (C2), 55.0 ($NHCH_2$), 61.8 (C1); HRMS (ESI) calcd for $C_{10}H_{23}N_2$ $[M+H]^+$ 171.1861, found 171.1850. Anal. Calcd (%) for $C_{10}H_{24}Cl_2N_2$: C, 49.38; H, 9.95; N, 11.52. Found: C, 49.32; H, 9.97; N, 11.43.

(1*R*,2*R*)-N^1-*sec*-Butylcyclohexane-1,2-diamine dihydrochloride (**3d**.2HCl)

White powder; yield 7.39 g, 76%; $[\alpha]_D^{25} = -39.6$ (c 0.44, H_2O); IR (KBr) $\upsilon = 2938$, 2866, 1596, 1553, 1502, 1450, 1031 cm^{-1}; ^1H NMR (300 MHz, D_2O, 25°C) $\delta = 0.94$–1.01 (m, 3H, CH_3CH_2), 1.30–1.32 (m, 3H, CH_3CH), 1.35–1.41 (m, 2H, CH_3CH_2), 1.44–2.29 (m, 8H, CH_2 of DACH), 3.39–3.43 (m, 1H, CH_3CH), 3.44–3.51 (m, 2H, NHC*H* and NH_2CH); ^{13}C NMR (75 MHz, D_2O, 25°C) $\delta = 11.8$ (CH_2CH_3), 16.5 ($CHCH_3$), 25.1 (C4), 25.4 (C5), 28.8 (C6), 29.4 ($CHCH_2$), 32.2 (C3), 54.4 ($CHCH_3$), 56.6 (C1), 58.2 (C2); HRMS (ESI) calcd for $C_{10}H_{23}N_2$ $[M+H]^+$ 171.1861, found 171.1852. Anal. Calcd (%) for $C_{10}H_{24}Cl_2N_2$: C, 49.38; H, 9.95; N, 11.52. Found: C, 49.44; H, 10.04; N, 11.55.

(1*R*,2*R*)-N^1-*n*-Pentylcyclohexane-1,2-diamine dihydrochloride (**3e**.2HCl)

White powder; yield 8.44 g, 82%; $[\alpha]_D^{25} = -38.7$ (c 0.54, H_2O); IR (KBr) $\upsilon = 3420$, 2947, 1615, 1579, 1509, 1444, 1032 cm^{-1}; ^1H NMR (500 MHz, D_2O, 25°C) $\delta = 0.88$ (t, 3H, $J = 6.9$ Hz, CH_3), 1.34–1.42 (m, 6H, $CH_2CH_2CH_2CH_3$), 1.48–2.30 (m, 8H, CH_2 of DACH), 2.99–3.27 (m, 2H, NHC*H* and NH_2CH), 3.36–3.51 (m, 1H, $NHCH(CH_3)_2$); ^{13}C NMR (75 MHz, D_2O, 25°C) $\delta = 15.8$ (CH_3), 24.1 (CH_3CH_2), 25.1 (C4), 25.2 (C5), 28.0 (C6), 28.8 ($CH_3CH_2CH_2$), 30.5 ($NHCH_2CH_2$), 32.0 (C3), 48.1 ($NHCH_2$), 54.0 (C2), 61.0 (C1); HRMS (ESI) calcd for $C_{11}H_{25}N_2$ $[M+H]^+$ 185.2018, found 185.2012. Anal. Calcd (%) for $C_{11}H_{26}Cl_2N_2$: C, 51.36; H, 10.19; N, 10.89. Found: C, 51.42; H, 10.21; N, 10.94.

(1*R*,2*R*)-N^1-(Pentan-3-yl)cyclohexane-1,2-diamine dihydrochloride (**3f**.2HCl)

White powder; yield 4.32 g, 42%; $[\alpha]_D^{25} = -55.2$ (c 0.63, H_2O); IR (KBr) $\upsilon = 3421$, 2944, 1604, 1575, 1519, 1456, 1025 cm^{-1}; ^1H NMR (300 MHz, D_2O, 25°C) $\delta = 0.93$–1.01 (m, 6H, CH_2CH_3), 1.30–2.35 (m, 12H, CH_3CH_2 and CH_2 of DACH), 3.34-3.65 (m, 3H, NHC*H* and NH_2CH); ^{13}C NMR (75 MHz, D_2O, 25°C) $\delta = 10.8$ (CH_3), 11.1 (CH_3), 23.3 (C4), 25.0 (C5), 25.4 (CH_3CH_2), 25.6 (CH_3CH_2), 29.1 (C6), 32.1 (C3), 54.3 (C2), 58.8 (C1), 61.6 (CH_3CH_2CH); HRMS (ESI) calcd for $C_{11}H_{25}N_2$ $[M+H]^+$ 185.2012, found 185.2011.Anal. Calcd (%) for $C_{11}H_{26}Cl_2N_2$: C, 51.36; H, 10.19; N, 10.89. Found: C, 51.44; H, 10.25; N, 10.92.

(1R,2R)-N^1-(4-Methylpentan-2-yl)cyclohexane-1,2-diamine dihydrochloride (**3g**.2HCl)

White powder; yield 5.43 g, 50%; $[\alpha]_D^{25} = -52.9$ (c 0.52, H_2O); IR (KBr) $\upsilon = 3421$, 2956, 2869, 1576, 1519, 1451, 1023 cm^{-1}; ^1H NMR (300 MHz, D_2O, 25°C) $\delta = 0.89$-0.97 (m, 6H, $CH(CH_3)_2$), 1.31 (d, 3H, $J = 6.5$ Hz, $NHCHCH_3$), 1.35–2.35 (m, 11H, CH_3CH and CH_2 of DACH), 3.36–3.58 (m, 3H, NHCH and NH_2CH); ^{13}C NMR (75 MHz, D_2O, 25°C) $\delta = 17.0$ (2C, $CH(CH_3)_2$), 23.0 ($NHCHCH_3$), 25.1 (C4), 25.3 (C5), 26.7 ($CH(CH_3)_2$), 28.7 (C6), 32.1 (C3), 45.0 ($NHCHCH_3$), 53.7 (CH_3CHCH_2), 54.4 (C1), 58.1 (C2); HRMS (ESI) calcd for $C_{12}H_{27}N_2$ $[M+H]^+$ 199.2169, found 199.2162. Anal. Calcd (%) for $C_{12}H_{28}Cl_2N_2$: C, 53.13; H, 10.40; N, 10.33. Found: C, 53.11; H, 10.35; N, 10.26.

(1R,2R)-N^1-Neopentylcyclohexane-1,2-diamine dihydrochloride (**3h**.2HCl)

White powder; yield 8.64 g, 84%; $[\alpha]_D^{25} = -30.6$ (c 0.52, H_2O); IR (KBr) $\upsilon = 3434$, 2945, 1611, 1518, 1453, 1029 cm^{-1}; ^1H NMR (300 MHz, D_2O, 25°C) $\delta = 1.05$ (s, 9H, $C(CH_3)_3$), 1.31–2.36 (m, 8H, CH_2 of DACH), 2.92–3.16 (m, 2H, $NHCH_2$), 3.37–3.59 (m, 2H, NHCH and NH_2CH); ^{13}C NMR (75 MHz, D_2O, 25°C) $\delta = 25.3$ (C4), 25.4 (C5), 29.0 (C6), 31.9 (C3), 32.6 (3C, CH_3), 53.6 ($NHCH_2CH$), 54.9 ($NHCH_2$), 59.2 (C2), 62.5 (C1); HRMS (ESI) calcd for $C_{11}H_{25}N_2$ $[M+H]^+$ 185.2012, found 185.2010. Anal. Calcd (%) for $C_{11}H_{26}Cl_2N_2$: C, 51.36; H, 10.19; N, 10.89. Found: C, 51.42; H, 10.27; N, 10.89.

(1R,2R)-N^1-Cyclopentylcyclohexane-1,2-diamine dihydrochloride (**3i**.2HCl)

White powder; yield 7.15 g, 70%; $[\alpha]_D^{25} = -37.0$ (c 0.44, H_2O); IR (KBr) $\upsilon = 3430$, 2940, 2869, 1613, 1506, 1452, 1030 cm^{-1}; ^1H NMR (300 MHz, D_2O, 25°C) $\delta = 1.11$-2.59 (m, 16H, CH_2 of DACH and cyclopentyl), 3.40–3.47 (m, 3H, NHCH and NH_2CH); ^{13}C NMR (75 MHz, D_2O, 25°C) $\delta = 24.4$ ($CHCH_2CH_2$, cyclopentyl), 24.5 ($CHCH_2CH_2$, cyclopentyl), 25.8 (C4), 25.9 (C5), 28.5 (C6), 30.8 ($CHCH_2CH_2$, cyclopentyl), 31.4 ($CHCH_2CH_2$, cyclopentyl), 32.2 (C3), 53.9 (NHCH, cyclopentyl), 59.4 (C2), 59.5 (C1); HRMS (ESI) calcd for $C_{11}H_{23}N_2$ $[M+H]^+$ 183.1856, found 183.1846. Anal. Calcd (%) for $C_{11}H_{24}Cl_2N_2$: C, 51.76; H, 9.48; N, 10.98. Found: C, 51.71; H, 9.41; N, 10.91.

(1R,2R)-N^1-*n*-Hexylcyclohexane-1,2-diamine dihydrochloride (**3j**.2HCl)

White powder; yield 8.79 g, 81%; $[\alpha]_D^{25} = -39.9$ (c 0.52, H_2O); IR (KBr) $\upsilon = 3430$, 2935, 2863, 1575, 1519, 1456, 1024 cm^{-1}; ^1H NMR (300 MHz, D_2O, 25°C) $\delta = 0.86$ (t, 3H, $J = 6.9$ Hz, CH_2CH_3), 1.29–2.30 (m, 16H, $CH_3CH_2CH_2CH_2CH_2$ and CH_2 of DACH), 3.00–3.51 (m, 4H, $NHCH_2$ and NH_2CH); ^{13}C NMR (75 MHz, D_2O, 25°C) $\delta = 16.1$ (CH_3), 24.4 (CH_3CH_2), 25.1 (C4), 25.2 (C5), 28.1 ($NHCH_2CH_2CH_2$), 28.2 (C6), 28.8 ($NHCH_2CH_2$), 32.0 ($CH_3CH_2CH_2$), 33.1 (C3), 48.1 ($NHCH_2$), 54.0 (C2), 61.0 (C1); HRMS (ESI) calcd for $C_{12}H_{27}N_2$ $[M+H]^+$ 199.2169, found 199.2160. Anal. Calcd (%) for $C_{12}H_{28}Cl_2N_2$: C, 53.13; H, 10.40; N, 10.33. Found: C, 53.11; H, 10.37; N, 10.30.

(1R,2R)-N^1-(Hexan-2-yl)cyclohexane-1,2-diamine dihydrochloride (**3k**.2HCl)

White powder; yield 7.70 g, 71%; $[\alpha]_D^{25} = -53.9$ (c 0.41, H_2O); IR (KBr) $\upsilon = 3411$, 2941, 2867, 1579, 1521, 1454, 1027 cm^{-1}; ^1H NMR (500 MHz, D_2O, 25°C) $\delta = 0.89$ (t, 3H, $J = 7.1$ Hz, CH_2CH_3), 1.32 (d, 3H, $J = 6.5$ Hz, $CHCH_3$), 1.33–2.30 (m, 14H, $CH_3CH_2CH_2CH_2$ and CH_2 of DACH), 3.44–3.54 (m, 3H, $NHCH_2$ and NH_2CH); ^{13}C NMR (75 MHz, D_2O, 25°C) $\delta = 15.7$ (CH_2CH_3), 17.1 ($CHCH_3$), 24.4 (CH_3CH_2), 25.1 (C4), 25.4 (C5), 28.8 ($CH_3CH_2CH_2$), 29.5 (C6), 32.2 (C3), 35.8 (CH_3CHCH_2), 54.4 ($NHCHCH_3$), 55.4 (C2), 58.2 (C1); HRMS (ESI) calcd for $C_{12}H_{27}N_2$ $[M+H]^+$ 199.2169, found 199.2161. Anal. Calcd (%) for $C_{12}H_{28}Cl_2N_2$: C, 53.13; H, 10.40; N, 10.33. Found: C, 53.13; H, 10.36; N, 10.28.

(1R,2R)-N^1-Cyclohexylcyclohexane-1,2-diamine dihydrochloride (**3l**.2HCl)

White powder; yield 8.51 g, 79%; $[\alpha]_D^{25} = -39.5$ (c 0.44, H_2O); IR (KBr) $\upsilon = 3429$, 2939, 2860, 1519, 1452, 1030 cm^{-1}; ^1H NMR (300 MHz, D_2O, 25°C) $\delta = 1.14$–2.32 (m, 18H, CH_2 of DACH and cyclohexyl), 3.34–3.65 (m, 3H, NHCH and NH_2CH); ^{13}C NMR (75 MHz, D_2O, 25°C) $\delta = 25.0$ (C4), 26.4 (C5), 26.7 (2C, $CHCH_2CH_2$, N^1-cyclohexyl), 27.0 ($CHCH_2CH_2CH_2$, N^1-cyclohexyl), 28.9 (C6), 30.1 ($CHCH_2$, N^1-cyclohexyl), 32.1 ($CHCH_2$, N^1-cyclohexyl), 32.5 (C3), 54.3 (C2), 57.5 (CH, N^1-cyclohexyl), 57.8 (C1); HRMS (ESI) calcd for $C_{12}H_{25}N_2$ $[M+H]^+$ 197.2012, found 197.2004. Anal. Calcd (%) for $C_{12}H_{26}Cl_2N_2$: C, 53.53; H, 9.73; N, 10.40. Found: C, 53.56; H, 9.77; N, 10.44.

(1R,2R)-N^1-(Heptan-2-yl)cyclohexane-1,2-diamine dihydrochloride (**3m**.2HCl)

White powder; yield 7.19 g, 63%; $[\alpha]_D^{25} = -46.4$ (c 0.53, H_2O); IR (KBr) $\upsilon = 3375$, 2937, 2865, 1590, 1519, 1452, 1029 cm^{-1}; ^1H NMR (500 MHz, D_2O, 25°C) $\delta = 0.86$ (s, 3H, CH_2CH_3), 1.31 (d, 3H, $J = 6.1$ Hz, $CHCH_3$), 1.35–2.31 (m, 16H, $CH_3CH_2CH_2CH_2CH_2$ and CH_2 of DACH), 3.37–3.52 (m, 3H, $NHCH_2$ and NH_2CH); ^{13}C NMR (125 MHz, D_2O, 25 °C) $\delta = 15.5$ (CH_3), 16.7 ($NHCHCH_3$), 18.8 (CH_3CH_2), 23.9 (C4), 24.7 (C5), 26.6 ($CH_3CH_2CH_2CH_2$), 28.4 (C6), 31.5 ($CH_3CH_2CH_2$), 32.8 (C3), 35.6 (CH_3CHCH_2), 54.0 ($NHCHCH_3$), 55.0 (C2), 57.8 (C1); HRMS (ESI) calcd for $C_{13}H_{29}N_2$ $[M+H]^+$ 213.2325, found 213.2336. Anal. Calcd (%) for $C_{13}H_{30}Cl_2N_2$: C, 54.73; H, 10.60; N, 9.82. Found: C, 53.76; H, 10.64; N, 9.84.

(1R,2R)-N^1-(Octan-3-yl)cyclohexane-1,2-diamine dihydrochloride (**3n**.2HCl)

White powder; yield 5.63 g, 47%; $[\alpha]_D^{25} = -27.0$ (c 0.60, H_2O); IR (KBr) $\upsilon = 3435$, 2937, 2863, 1592, 1499, 1450, 1029 cm^{-1}; ^1H NMR (300 MHz, D_2O, 25°C) $\delta = 0.87$ (s, 3H, $CH_2CH_2CH_3$), 0.91–1.01 (m, 3H, $CHCH_2CH_3$), 1.33–2.34 (m, 18H, $CH_3CH_2CH_2CH_2CH_2$, CH_3CH_2CH and CH_2 of DACH), 3.35–3.48 (m, 3H, $NHCH_2$ and NH_2CH); ^{13}C NMR (75 MHz, D_2O, 25°C) $\delta = 10.9$ (CH_3CH_2CH), 11.2 ($CH_3CH_2CH_2$), 16.0 ($CH_3CH_2CH_2$), 24.4 ($CH_3CH_2CH_2CH_2$), 25.1 (C4), 25.4 (C5), 26.5 (CH_3CH_2CH), 29.2 (C6), 32.0 ($CH_3CH_2CH_2$), 32.2 ($CH_3CH_2CH_2CH_2CH_2$), 33.4 (C3), 54.3 (C2), 54.9 (CH_3CH_2CH), 58.9 (C1); HRMS (ESI) calcd for $C_{14}H_{31}N_2$ $[M+H]^+$ 227.2482, found 227.2476.Anal. Calcd (%) for $C_{14}H_{32}Cl_2N_2$: C, 56.18; H, 10.78; N, 9.36. Found: C, 56.16; H, 10.72; N, 9.31.

(1R,2R)-N^1-(Undecan-2-yl)cyclohexane-1,2-diamine dihydrochloride (**3o**.2HCl)

White powder; yield 6.42 g, 47%; $[\alpha]_D^{25} = -31.6$ (c 0.56, H_2O); IR (KBr) $\upsilon = 3403$, 2927, 2855, 1576, 1532, 1455, 1027 cm^{-1}; ^1H NMR (500 MHz, D_2O, 25°C) $\delta = 0.84$ (t, 3H, $J = 6.2$ Hz, CH_2CH_3), 1.26 (s, 3H, $CHCH_3$), 1.30–2.27 (m, 24H, $CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$ and CH_2 of DACH), 3.38–3.51 (m, 3H, $NHCH_2$ and NH_2CH); ^{13}C NMR (75 MHz, D_2O, 25 °C) $\delta = 16.4$ (CH_3CH_2), 17.2 (CH_3CH), 19.5 (CH_3CH_2), 25.2 (C4), 25.3 (C5), 28.3 ($CH_3CHCH_2CH_2$), 28.9 (C6), 31.7 ($CH_3CH_2CH_2CH_2$), 31.8 ($CH_3CHCH_2CH_2CH_2CH_2$), 31.9 (CH_3CH_2-$CH_2CH_2CH_2CH_2$), 32.1 ($CH_3CHCH_2CH_2CH_2$), 32.2 ($CH_3CH_2CH_2$), 34.5 (C3), 36.2 (CH_3CHCH_2), 54.4 ($NHCHCH_3$), 54.8 (C2), 58.3 (C1); HRMS (ESI) calcd for $C_{17}H_{37}N_2$ $[M+H]^+$ 269.2951, found 269.2947. Anal. Calcd (%) for $C_{17}H_{38}Cl_2N_2$: C, 59.81; H, 11.22; N, 8.21. Found: C, 59.82; H, 11.24; N, 8.19.

General Procedure for the Henry Reaction

A test tube with a stirring bar was charged with a ligand (0.06 mmol, 12 mol%, **3**, free diamine (prepared from the corresponding

hydrochlorides **3**.2HCl), copper(II) acetate hydrate (10.0 mg, 0.05 mmol, 10 mol%), and *i*-PrOH (1.0 ml). The resulting suspension was gently heated for 30 s and stirred for 1 h to ensure completion of the complex formation. A solution of aldehyde (0.5 mmol, 1 equiv.) in *i*-PrOH (0.3 ml) was then added at 25°C. The whole mixture was cooled to −40°C for 15 min and treated with nitromethane (5.0 mmol, 10 equiv.) via a syringe. After 5 min, a solution of Et_3N (3.9 mg, 7.70 mol%) in *i*-PrOH (0.2 ml) was added via a syringe. The mixture was stirred for 24 h at −40°C. Purification by flash chromatography on silica gel (30 g, *n*-hexane–AcOEt; 4:1, v/v) afforded the desired β-nitroalcohols.

Acknowledgments

This work is supported by the National Natural Science Foundation of China (Project No. 21271041) and the New Drug Creation Project of the National Science and Technology Major Foundation of China (Project 2013ZX09402102-001-006). Li would like to thank the Scientific Research Innovation Project for College Graduates of Jiangsu Province (Project CXZZ12_0118).

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