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The development of new amine–amide ligands for application in Cu(II)-catalyzed enantioselective Henry reactions

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ABSTRACT

A new type of chiral tertiary amine ligand was designed and derived from L-proline and (*R*)-BINOL. These new chiral ligands chelated with Cu(II) showed highly catalytic efficiency in enantioselective Henry reactions. Excellent yields (up to 99%) and high enantioselectivities (up to 96% ee) were achieved for aromatic, hetero-aromatic and aliphatic aldehyde substrates, without an additional base additive or the need for air or moisture exclusion.

1. Introduction

To be a useful chiral catalyst, it must provide the target product in high yield and excellent enantioselectivity. Moreover, it must have a simple synthesis from commercially available starting materials. Many enzymes are remarkable asymmetric catalysts and show excellent activity and selectivity.[1] However, their complicated structures and specific selectivity mean that their applicability can be narrow. Aspiring to imitate the enzymatic synergistic cooperation of multi-active centers, chemists set out to design and develop many types of useful multifunctional catalysts for asymmetric synthesis from a fundamental backbone.[2] It is even more surprising that certain classes of synthetic catalysts are enantioselective over a wide range of different reactions; such catalysts can be called 'privileged structures'.[3] Among them, (*S*)-proline, and (*R*)- and (*S*)-BINOL are some of the most interesting catalyst structures.[4] Recently, researchers have been actively pursuing the design of new ligands by exploiting the concept derived from multifunctional catalysts. Many homochiral catalysts containing amines, ethers, alcohol etc. as electron donors have been successfully developed.[5]

(*S*)-Proline features as a bifunctional organocatalyst.[4c,d] After simple modification of proline to prolinamide, similar to some small peptides catalysts,[6] the amide functional group could assist the reactions efficiently and selectively. Moreover, these systems permit the enhancement of the structural diversity of the catalysts and thus the ability to finely tune their reactivity. For the binaphthalene fragment, it could provide a restricted rotation around the biaryl axis due to the steric hindrance of the aryl group. The modification of this binaphthyl moiety would also allow further modification of the catalytic activity. Therefore, the design of a new multifunctional catalyst integrating the above separated moieties into one molecule would be attractive. Nájera et al.[7] developed and synthesized new types of prolinamides derived from a binaphthalene backbone and (*S*)-proline, as shown in Scheme 1 (BINAM-prolinamide). However, this catalyst is still a base-reliant type organocatalyst. The carboxylic group of proline formed a prolinamide directly with 2,2′-diamino-1,1′-binaphthalene, which would restrict its nature of structural diversity. In terms of economy and flexibility, modification of (*S*)-proline would be much easier than that of binaphthalene. Moreover, the chiral ligand could further expand upon its application with bonds to different metal centers. Herein our aim was to find a new type of chiral ligand based on the idea of integrating binaphthyl and proline moieties into one molecule connected through a simple linker, as shown in Scheme 1 (L).

The Henry reaction is one of the most atom economical carbon–carbon bond forming reactions.[8] The resulting *β*-hydroxy nitro compounds re widely used in synthetic chemistry.[9] Over the past few years, many amine and amide type chiral ligands have been successfully applied in asymmetric Henry reactions.[10] However, many of these catalytic systems still suffer from limitations such as high catalyst loading, air- and moisture-sensitivity, and additional stoichiometric base additives. Herein, we report the synthesis of new chiral tertiary amines and amide type ligands simply derived from (*S*)-proline and (*R*)-BINOL, as well as their successful application as chiral ligands in Cu(II) catalyzed asymmetric Henry reactions. Excellent yields (up to 99%) and enantioselectivities (up to 96%) were obtained for aromatic, hetero-aromatic and aliphatic

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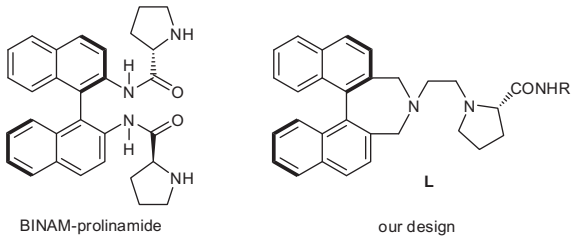


Scheme 1. BINAM-prolinamide and a new design of chiral ligands.

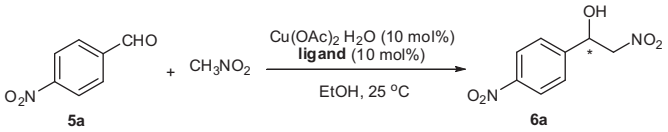
aldehyde substrates, without the need for an extra base additive or the need for air or moisture exclusion.

2. Results and discussion

With the aim of discovering a simple, inexpensive and efficient route to combine (*S*)-proline and (*R*)-BINOL into one molecule, a series of chiral tertiary amine type ligands **L1**–**L5** were synthesized from commercially available (*S*)-Boc-proline and (*R*)-BINOL via the pathways outlined in Scheme 2. Our synthesis began by transforming (*S*)-Boc-proline into the corresponding amides. Cleavage of the *N*-Boc protecting group with trifluoroacetic acid in dichloromethane gave **1**.[11] It is known that tertiary diamine ligands have relatively strong basicity and coordination ability, which would influence the catalytic activity. Therefore in our design strategy, the linker between the proline and binaphthyl structure is the key feature. *N*-Cbz-2-bromoethylamine was finally chosen to play the role of bridging linker. After alkylation with amides **1**, the *N*-Cbz protecting group was removed to obtain **2** by hydrogenolysis under a hydrogen atmosphere at ordinary pressure in the presence of 10% palladium on a carbon catalyst. Meanwhile, (*R*)-BINOL was transferred to a bis-triflate protected species with trifluoromethanesulfonic anhydride. Subsequent cross-coupling with methylmagnesium bromide in the presence of the nickel catalyst $NiCl_2(PPh_3)_2$ afforded the (*R*)-dimethylated compound **3**. The route to obtain bis(bromomethyl)binaphthalene **4** involves the use of NBS in cyclohexane using benzoyl peroxide as a radical initiator.[12] The final step was a double-alkylation between **4** and **2** to achieve chiral ligands **L1**–**L5**.[10b,13]

With the chiral ligands in hand, we were then able to test their effectiveness in asymmetric Henry reactions. Copper(II) acetate monohydrate [$Cu(OAc)_2{\cdot}H_2O$] was chosen for screening the new chiral ligands in ethanol at room temperature to catalyze the model reaction between 4-nitrobenzaldehyde **5a** and nitromethane. The results are listed in Table 1 (entries 1 to 5); **L5** was found to be the best for this reaction, affording the desired product in near quantitative yield with 80% ee after 24 h (Table 1, entry 5). Ligand **L4** with a phenyl group produced the same near quantitative yield, but with lower enantioselectivity (Table 1, entry 4). For the rest **L1**–**L3** with aliphatic R groups, only about 10% ee was obtained (Table 1, entries 1 to 3).

Table 1
Chiral ligands screening in asymmetric Henry reaction

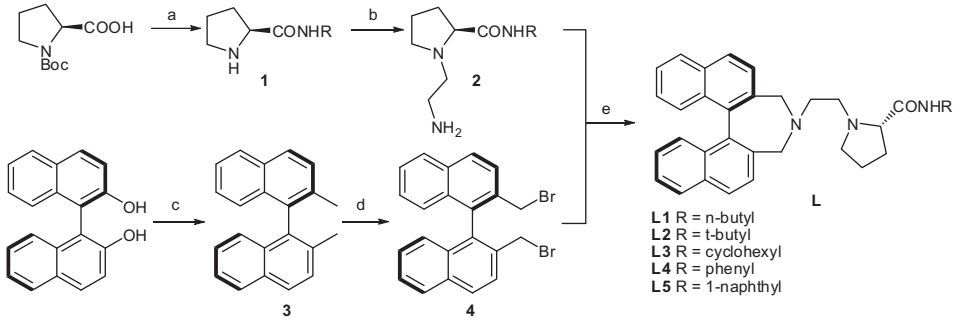


Entry[a]	Ligand	Time [h]	% Yield[b]	% *ee*[c]
1	**L1**	24	85	9 (*R*)
2	**L2**	24	90	13 (*R*)
3	**L3**	24	83	10 (*R*)
4	**L4**	24	99	77 (*R*)
5	**L5**	24	98	80 (*R*)
6	**L6**	24	84	17 (*R*)
7	**L7**	24	83	31 (*R*)

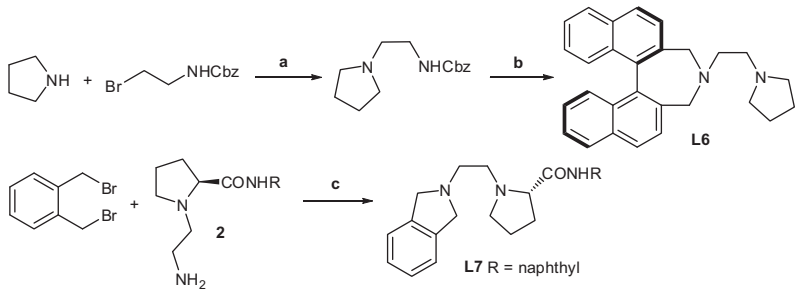
[a] Reactions were carried out on a 0.5 mmol scale of nitrobenzaldehyde with nitromethane (10 equiv) in EtOH (1 mL) in the presence of ligand (10 mol %) Cu $(OAc)_2{\cdot}H_2O$ (10 mol %) at room temperature.
[b] Isolated yield.
[c] Enantiomeric excess were determined by HPLC analysis. The absolute configurations were established by comparison of the sign of the specific rotation values with that in the literature.[14]

From the above experimental results, we determined that the reactivity and enantioselectivity of chiral ligands were closely dependent on the R substituents of the amide moiety. In order to determine further information about each fragment's function for asymmetric induction, we synthesized two comparison ligands **L6** and **L7** and tested them in the model reaction (Scheme 3). Removing the chiral part of (*S*)-proline, **L6** showed only 17% enantioselectivity. After replacement of the binaphthyl fragment with iso-indoline, **L7** only afforded 31% enantioselectivity. These results suggest that both the amide moiety of (*S*)-proline and the binaphthyl units in chiral ligand play a pivotal role in the asymmetric induction, among which the amide moiety is more important than the binaphthyl units. It is evident that we can modify the aromatic amide moiety with a priority to improve the activity and enantioselectivity in the future work.

Encouraged by the initial results in the asymmetric Henry reaction, we continued the optimization of the reaction conditions. First, a series of metal salts were evaluated in combination with chiral ligand **L5** and in ethanol at 25 °C over 24 h to catalyze the model reaction. The results are shown in Table 2 (entries 1 to 7). The other divalent metal salts, such as $Zn(OAc)_2{\cdot}2H_2O$, $Co(OAc)_2{\cdot}4H_2O$, $Ni(OAc)_2{\cdot}4H_2O$ and $Cu(acac)_2$, gave the same high yield, but no enantioselectivity (Table 2, entries 2 to 5). Furthermore

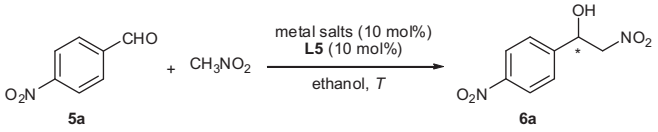


Scheme 2. Synthetic routes to chiral ligands: (a) (i) RNH_2, $ClCO_2{}^iBu$, Et_3N, 0 °C–rt, (ii) TFA, CH_2Cl_2, rt; (b) (i) BrC_2H_4NHCbz, K_2CO_3, CH_3CN, reflux, (ii) Pd/C, H_2, MeOH, rt; (c) (i) Tf_2O, Py, CH_2Cl_2, 0 °C, (ii) MeMgBr, $NiCl_2(PPh_3)_2$, 0 °C; (d) NBS, $(PhCO)_2O$, cyclohexane, reflux; (e) Et_3N, CH_2Cl_2, reflux.



Scheme 3. Synthetic routes to comparison ligands **L6** and **L7**: (a) K_2CO_3, CH_3CN, reflux; (b) (i) Pd/C, H_2, MeOH, rt, (ii) **4**, Et_3N, DCM, reflux; (c) Et_3N, DCM, reflux.

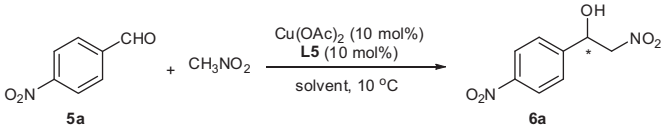
Table 2
Optimization on metal ions and temperature



Entry[a]	Metal salts	*T* (°C)	% Yield[b]	% *ee*[c]
1	$Cu(OAc)_2{\cdot}H_2O$	25	98	80 (*R*)
2	$Zn(OAc)_2{\cdot}2H_2O$	25	95	0
3	$Co(OAc)_2{\cdot}4H_2O$	25	95	0
4	$Ni(OAc)_2{\cdot}4H_2O$	25	93	0
5	$Cu(acac)_2$	25	92	0
6	$Cu(OTf)_2$	25	NR	—
7	CuI	25	90	16 (*R*)
8	CuOAc	25	90	36 (*R*)
9	$Cu(OAc)_2$	25	98	84 (*R*)
10	$Cu(OAc)_2$	20	89	87 (*R*)
11	$Cu(OAc)_2$	10	95	93 (*R*)
12	$Cu(OAc)_2$	0	60	87 (*R*)
13	$Cu(OAc)_2$	−10	NR	—

[a] Reactions were carried out on a 0.5 mmol scale of nitrobenzaldehyde with nitromethane (10 equiv) in EtOH (1 mL) in the presence of **L5** (10 mol %) metal salts (10 mol %) for 24 h.
[b] Isolated yield.
[c] Enantiomeric excess was determined by HPLC analysis. The absolute configurations were established by comparison of the sign of the specific rotation values with that in the literature.[14]

Table 3
Optimization of the reaction conditions



Entry[a]	Solvent	Time [h]	% Yield[b]	% *ee*[c]
1	EtOH	36	99	96 (*R*)
2	^{i}PrOH	36	95	90 (*R*)
3	MeOH	36	90	92 (*R*)
4	THF	36	95	88 (*R*)
5	Et_2O	36	75	85 (*R*)
6	MeCN	36	70	85 (*R*)
7	Toluene	36	72	88 (*R*)
8	CH_2Cl_2	36	29	89 (*R*)
9	EtOH	24	95	93 (*R*)
10[d]	EtOH	24	92	82 (*R*)
11[e]	EtOH	24	93	94 (*R*)
12[f]	EtOH	48	65	90 (*R*)
13[g]	EtOH	48	63	82 (*R*)

[a] Reactions were carried out on a 0.5 mmol scale of nitrobenzaldehyde with nitromethane (10 equiv) in solvent (1 mL) in the presence of **L5** (10 mol %) $Cu(OAc)_2$ (10 mol %) at room temperature.
[b] Isolated yield.
[c] Enantiomeric excess was determined by HPLC analysis. The absolute configurations were established by comparison of the sign of the specific rotation values with that in the literature.[14]
[d] Et_3N (1.0 equiv) was used.
[e] 3 Å MS (0.2 g/mmol) was added.
[f] **L5** (5 mol %) and $Cu(OAc)_2$ (5 mol %) were used.
[g] **L5** (1 mol %) and $Cu(OAc)_2$ (1 mol %) were used.

when using $Cu(OTf)_2$, the reaction did not take place (Table 2, entry 6). As well as divalent copper salts, monovalent copper salts CuI and CuOAc also promoted the reaction with satisfactory yield, but the enantioselectivities dropped dramatically (Table 2, entries 7 and 8). Similar with $Cu(OAc)_2{\cdot}H_2O$, the $Cu(OAc)_2$ could promote the reaction smoothly in high yield and with an even higher ee value of 84% (Table 2, entry 9). In terms of yield and enantioselectivity, $Cu(OAc)_2$ proved to be the preferred catalyst. Next, we optimized the temperature (Table 2, entries 10 to 13). Decreasing the temperature to 10 °C enhanced the enantioselectivity to 93%, while still keeping with high yield (Table 2, entry 11).

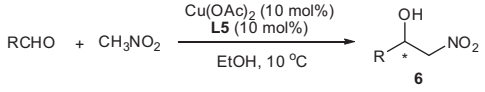
Next, the solvent effect on the enantioselectivity was examined and the results are shown in Table 3. When the alcohol solvents such as ^{i}PrOH, EtOH, and MeOH were used, all of the reactions proceeded smoothly to afford the desired product **6a** with high yields (up to 99%) and high enantioselectivities (up to 96% ee) (Table 3, entries 1 to 3). It was worth noting that EtOH still resulted in a higher ee than any other solvents (Table 3, entry 1). Using THF as the solvent, the reaction gave the desired Henry product **6a** in 95% yield and with 88% ee (Table 3, entry 4). When toluene, Et_2O and MeCN were used as solvents, the reaction resulted in good yield (70% to 75%) and with high enantioselectivity (up to 88% ee) (Table 3, entries 5 to 7). Unfortunately, when CH_2Cl_2 was used as the solvent, it gave product **6a** with only 29% yield and 89% ee (Table 3, entry 8). The above results indicated that ethanol was the preferred solvent for this Henry reaction. A Lewis base can play a role in the activation of the substrate.[15] Et_3N was tested as an additive, but unfortunately the enantioselectivity dropped to 82% (Table 3, entry 10). As in previous metal salt screening, $Cu(OAc)_2$ gave higher enantioselectivity than $Cu(OAc)_2{\cdot}H_2O$. Hence we speculated that the hydrate might have some influence on the enantioselectivity. The molecular sieves additive was tested in this reaction (0.2 g/mmol 3 Å MS). However there was no obvious improvement in the enantioselectivity, which meant that this reaction was not moisture sensitive (Table 3, entry 11). When the reaction time was prolonged, it could enhance the yield and enantioselectivity (Table 3, entry 1, 9). Catalyst loading was also tested; 5 mol % of $Cu(OAc)_2$ and **L5** resulted in high ee (90%) but the yield decreased dramatically (Table 3, entry 12). Even lower catalyst loading (1 mol %) was also tested, and comparable enantioselectivity (82%) could still be achieved (Table 3, entry 13).

With the optimized condition in hand, we next studied the generality of the asymmetric Henry reaction of various aromatic aldehydes and aliphatic aldehydes with nitromethane in the

presence of catalyst **L5** with $Cu(OAc)_2$ as shown in Table 4. The scope of our catalyst system was extended to aromatic aldehydes (Table 4, entries 1 to 13), which provided high yields (up to 99%) and excellent enantioselectivities (up to 96% ee). The reactions of benzaldehydes substituted with electron-donating groups afforded Henry adducts **6d** and **6g** in lower yields than **6c** (Table 4, entries 4, 7). Conversely, electron-withdrawing substituents made the yield higher (Table 4, entries 1, 2, and 10). Although the electronic properties of the substituents on the aromatic ring affected the yield, they had little influence on the enantioselectivity. In addition, a variety of 2-, 3-, or 4-substituted benzaldehydes (Table 4, entries 4 to 9) 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 effect of our system. Other aromatic aldehydes, 1-naphthaldehyde and 2-naphthaldehydes, were found to be suitable substrates, and the reaction afforded the desired Henry products **6k** to **6l** in high yields (82%, 83%) and enantioselectivities (90%, 88% ee) (Table 4, entries 11, 12). The heteroaromatic aldehydes also reacted with nitromethane in our catalytic system to give optically active nitroaldol adducts **6m** in good yield and with good enantioselectivity (Table 4, entry 13). Under the same reaction conditions, a variety of aliphatic aldehydes were obtained in good yields (up to 91%) as well as with excellent enantioselectivities ranging from 88% to 93%, which produced their respective β-nitroalcohols. It should be noted that the length and the size of the alkyl chains in the substrates, no matter if they were unbranched (Table 4, entries 14 to 20), branched (Table 4, entry 17) alkyl chain aldehydes, they had hardly any influence on the enantioselectivity or the yield of the resulting product derived from aliphatic aldehydes.

In view to explore the nitroalkane substrate scope, we also tested some other nitroalkanes. The corresponding nitroaldol adducts bearing two stereogenic centers were obtained in good yield albeit moderate diastereoselectivities favoring *syn*-product and enantioselectivities were observed. Diastereoselectivity was improved when more sterically hindered aldehyde was used (Table 5, entries 1 to 3). The limitation was the bad enantioselectivity of each diastereomer.

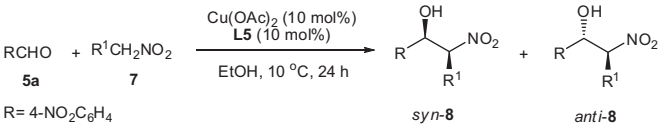
Table 4
Asymmetric catalysis Henry reactions



Entry[a]	R	Time (h)	% Yield[b]	% *ee*[c]
1	4-$NO_2C_6H_4$ **5a**	36	99	96 (*R*)
2	3-$NO_2C_6H_4$ **5b**	36	95	80 (*R*)
3	Phenyl **5c**	36	90	81 (*R*)
4	4-$MeOC_6H_4$ **5d**	48	85	87 (*R*)
5	2-$MeOC_6H_4$ **5e**	48	83	87 (*R*)
6	3-$MeOC_6H_4$ **5f**	48	89	89 (*R*)
7	4-MeC_6H_4 **5g**	48	83	83 (*R*)
8	2-MeC_6H_4 **5h**	48	80	69 (*R*)
9	3-MeC_6H_4 **5i**	48	83	75 (*R*)
10	4-BrC_6H_4 **5j**	48	92	80 (*R*)
11	1-Naphthyl **5k**	48	82	90 (*R*)
12	2-Naphthyl **5l**	48	83	88 (*R*)
13	2-thienyl **5m**	48	80	85 (*S*)
14	CH_3CH_2 **5n**	48	83	89 (NA)
15	$CH_3(CH_2)_2$ **5o**	48	91	93 (NA)
16	$CH_3(CH_2)_3$ **5p**	48	85	90 (*R*)
17	$(CH_3)_2CHCH_2$ **5q**	56	87	88 (*R*)
18	$CH_3(CH_2)_4$ **5r**	48	89	89 (*R*)
19	$CH_3(CH_2)_5$ **5s**	48	84	90 (*R*)
20	Cyclohexyl **5t**	36	81	90 (*R*)

[a] Reactions were carried out with aldehydes (0.5 mmol) and nitromethane (10 equiv) in EtOH (1 mL) in the presence of **L5** (10 mol %) and $Cu(OAc)_2$ (10 mol %).
[b] Isolated yield.
[c] Enantiomeric excess was determined by HPLC analysis. The absolute configurations were established by comparison of the sign of the specific rotation values with that in the literature.[14,16]

Table 5
Diastereoselective Henry reactions



Entry[a]	R^1	% Yield[b]	% *syn*/*anti*[c]	% *ee*[d]
1	Methyl **7a**	89	55/45	64/54
2	Ethyl **7b**	92	71/29	77/50
3	Benzyl **7c**	75	76/24	36/25

[a] Reactions were carried out with nitrobenzaldehyde (0.5 mmol) and nitroalkane (10 equiv) in EtOH (1 mL) in the presence of **L5** (10 mol %) and $Cu(OAc)_2$ (10 mol %).
[b] Isolated yield.
[c] Determined by ^1H NMR spectroscopy analysis.
[d] Enantiomeric excess was determined by HPLC analysis.

On the basis of the preliminary experimental findings and previously reported steric and electronic considerations,[10a,17] we have proposed a reasonable transition state model for the enantioselective Henry reaction (Fig. 1). The Cu(II) complex with a plane quadrilateral 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.[18] In the transition state, the two highly coordinative tertiary amine nitrogen atoms of **L5** occupy two neighboring strong coordination sites. Both the aldehyde and nitromethane are efficiently activated by coordination to the equatorial and the apical position of the copper atom, respectively. For maximum activation, the nucleophilic nitronate would orientate towards the inside position perpendicular to the ligand plane and be fixed with the hydrogen bonding with the N–H group of the amide moiety, whereas the electrophilic aldehyde should occupy the outside site, thus avoiding the steric hindrance of ligand **L5**. Therefore, the attack of the nitronate from the *Re*-face of the carbonyl group is hampered by one of the naphthyl structure moieties of the ligand, and so it takes place preferentially from the *Si*-face to give the nitroaldol with an (*R*)-configuration.

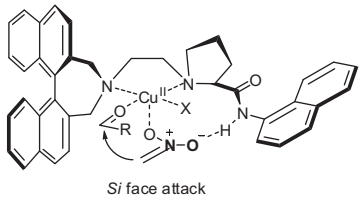


Figure 1. Proposed transition state for asymmetric Henry reaction.

3. Conclusions

In conclusion, we have designed and developed a series of new chiral amine ligands, which can be used to combine with copper(II) acetate as efficient catalysts for asymmetric Henry reactions. The results showed that most catalysts consisting of **L5**–$Cu(OAc)_2$ gave good yields and enantiomeric excess for the desired product. This catalyst system enables us to prepare β-nitroalcohols with good

enantioselectivities and high yields for a wide range of aldehydes including aliphatic, aromatic aldehydes, and heteroaromatic aldehydes. Further studies focusing on the modification of the ligands and their use as chiral ligands for other asymmetric reactions are currently under investigation in our laboratory.

4. Experimental

4.1. General

Starting materials, reagents, and dry solvent were purchased from commercial suppliers and used without further purification. Et_2O and THF were distilled from Na and benzophenone, Et_3N was dried from CaH_2. CH_2Cl_2 was distilled from CaH_2. Melting points (mp) were measured with melting point apparatus and which were uncorrected. Enantiomeric excesses (ee) were determined by HPLC using the corresponding commercial chiral column as stated in the experimental procedures at 23 °C and 25 °C with UV detector at 220 nm and 210 nm. Optical rotations were measured on a commercial polarimeter and are reported as follows: $[\alpha]_D^T$ (*c* g/100 mL, in solvent). ^1H NMR spectra were recorded on commercial instruments (400 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ = 7.26). Spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), integration and assignment. ^{13}C NMR spectra were collected on commercial instruments (100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from the tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$, δ = 77.0). HRMS was recorded on a commercial apparatus (ESI Source).

4.1.1. General synthetic procedures for (2*S*)-2-(2′-ethylamine)-pyrrolidine carboxamide 1

To a solution of L-*N*-Boc-proline (6.88 g, 32.0 mmol) in CH_2Cl_2 (240 mL) were added triethylamine (3.54 g, 35.2 mmol) and isobutyl chloroformate (4.64 g, 35.2 mmol) at 0 °C with stirring. After 15 min, amine (35.2 mmol) was added. The reaction was allowed to warm to room temperature and detected by TLC (Hexane/EtOAc = 4/1, v/v). The mixture was washed with 1 M $KHSO_4$, saturated $NaHCO_3$ and brine, then dried over anhydrous $MgSO_4$ and concentrated to give a crude product, which was further purified by silica-gel column chromatography (Hexane/EtOAc = 6/1, v/v).

The above product was dissolved in dry CH_2Cl_2 (16 mL) and treated with trifluoroacetic acid (16 mL). It was then stirred at room temperature for 3 h. The solvent was removed under vacuum, after which was added CH_2Cl_2 (10 mL). The pH value was brought into the range of 9–10 by the addition of 1 M NaOH. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$ and concentrated to give pure product **1**.

4.1.1.1. (*S*)-*N*-Butylpyrrolidine-2-carboxamide 1a. Brown oil (4.85 g, 89.2% yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.73 (s, 1H), 3.82 (dd, *J* = 27.2, 18.8 Hz, 1H), 3.25 (dd, *J* = 13.4, 6.8 Hz, 2H), 3.08 (dt, *J* = 10.2, 6.8 Hz, 1H), 2.96 (dt, *J* = 10.2, 6.3 Hz, 1H), 2.29–2.10 (m, 1H), 2.03–1.89 (m, 1H), 1.83–1.70 (m, 2H), 1.56–1.46 (m, 2H), 1.43–1.26 (m, 3H), 0.94 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.3, 61.5, 60.5, 47.2, 38.8, 31.7, 30.8, 26.1, 20.1, 13.8 ppm. $[\alpha]_D^{25}$ = −20.5 (*c* 1, MeOH).

4.1.1.2. (*S*)-*N*-(*tert*-Butyl)pyrrolidine-2-carboxamide 1b. White solid, (4.52 g, 83.1% yield), mp = 79–80 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50 (s, 1H), 3.65 (dd, *J* = 8.8, 5.6 Hz, 1H), 3.02 (dt, *J* = 10.1, 6.7 Hz, 1H), 2.90 (dt, *J* = 10.3, 6.4 Hz, 1H), 2.62 (d, *J* = 56.5 Hz, 1H), 2.12 (tt, *J* = 18.4, 9.0 Hz, 1H), 1.98–1.82 (m, 1H), 1.79–1.62 (m, 2H), 1.35 (t, *J* = 4.3 Hz, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.0, 61.2, 50.2, 47.2, 30.7, 28.8, 26.1 ppm. $[\alpha]_D^{25}$ = −15.6 (*c* 1, MeOH).

4.1.1.3. (*S*)-*N*-Cyclohexylpyrrolidine-2-carboxamide 1c. Brown oil (5.38 g, 85.7% yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 51.2 Hz, 1H), 3.81–3.63 (m, 2H), 3.01 (dt, *J* = 10.1, 6.8 Hz, 1H), 2.89 (dt, *J* = 10.2, 6.3 Hz, 1H), 2.19–2.04 (m, 2H), 1.95–1.79 (m, 3H), 1.75–1.65 (m, 4H), 1.64–1.55 (m, 1H), 1.44–1.30 (m, 2H), 1.23–1.09 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.0, 60.6, 47.3, 47.2, 33.2, 33.1, 30.8, 26.1, 25.6, 24.8, 24.8 ppm. $[\alpha]_D^{25}$ = −23.7 (*c* 1, MeOH).

4.1.1.4. (*S*)-*N*-Phenylpyrrolidine-2-carboxamide 1d. Yellow solid (5.26 g, 86.5% yield), mp = 76–77 °C [lit.[19]: 72 °C]. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.94 (s, 1H), 7.69–7.59 (m, 2H), 7.37–7.27 (m, 2H), 7.1–7.06 (m, 1H), 4.16–4.02 (m, 1H), 3.37 (s, 1H), 3.12 (dtd, *J* = 12.8, 10.4, 6.7 Hz, 2H), 2.36–2.15 (m, 1H), 2.07 (tt, *J* = 12.8, 6.2 Hz, 1H), 1.96–1.69 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 137.8, 129.0, 124.10, 119.5, 61.0, 47.3, 30.8, 26.0 ppm. $[\alpha]_D^{25}$ = −48.7 (*c* 1, ethanol).

4.1.1.5. (*S*)-*N*-(Naphthalen-1-yl)pyrrolidine-2-carboxamide 1e. Pale brown solid (6.78 g, 88.3% yield), mp = 62–65 °C [lit.[20]: 63–64 °C]. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.40 (s, 1H), 8.10 (t, *J* = 10.9 Hz, 1H), 7.67 (dd, *J* = 16.8, 7.9 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.38–7.24 (m, 3H), 3.78–3.65 (m, 1H), 2.93–2.73 (m, 2H), 2.25 (s, 1H), 2.12–1.80 (m, 2H), 1.67–1.42 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8, 134.0, 132.7, 128.7, 126.1, 126.0, 126.0, 125.9, 124.5, 120.3, 117.7, 61.5, 47.4, 30.9, 26.5 ppm. $[\alpha]_D^{31}$ = −14.6 (*c* 0.51, CH_2Cl_2) [lit.[19]: $[\alpha]_D^{25}$ = −7.3 (*c* 1, ethanol)].

4.1.2. General synthetic procedures for (2*S*)-2-(2′-ethylamine)-pyrrolidine carboxamide 2

To a solution of **1** (15.0 mmol) in CH_3CN (60 mL) were added K_2CO_3 (3.10 g, 22.5 mmol) and *N*-Cbz-2-bromoethylamine (3.87 g, 15.0 mmol) under stirring. It was then kept at 80 °C, and monitored by TLC (Hexane/EtOAc = 2/1, v/v). Next, K_2CO_3 was removed by filtration. The filtrate was concentrated to give a light brown oil. The oil was dissolved in ethyl acetate (150 mL) and the solution was washed with water (2 × 50 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude product. The residue was concentrated and purified by silica gel column chromatography (Hexane/EtOAc = 4/1, v/v) to give a white solid.

To a 50 mL three-necked flask was added the above product (30.00 mmol), which was dissolved in anhydrous MeOH (30 mL), after which 0.05 g Pd/C (10%, w/w) were added to the solution. The mixture was stirred at room temperature for 4 h under a hydrogen atmosphere. The reaction solution was filtered and the filtrate was concentrated under reduced pressure to afford **2** as a yellow oil. This compound was used directly in the next step.

4.1.3. General synthetic procedures for (*R*)-2,2′-dimethyl-1,1′-binaphthyl 3

To a solution of (*R*)-BINOL (14.3 g, 50 mmol) in 125 mL of CH_2Cl_2 was added pyridine (15.2 g, 150 mmol) followed by the dropwise addition of triflic anhydride (31.0 g, 110 mmol) at 0 °C. The mixture was then stirred at room temperature for 6 h. After removal of the solvent, the residue was diluted with EtOAc (100 mL) and then washed with 5% aqueous HCl (25 mL), saturated $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried over anhydrous sodium sulfate, concentrated and passed through a silica gel plug (Hexane/EtOAc = 10/1, v/v) to give the (*R*)-2,2′-bistriflate-1,1′-binaphthyl.

To a solution of (*R*)-bistriflate (4.57 g, 8.30 mmol) and $NiCl_2(PPh_3)_2$ (0.46 g, 0.70 mmol) in ether (80 mL) was added dropwise methyl magnesiumbromide (3.0 M in ether, 15 mL) at 0 °C. The reaction mixture was stirred at room temperature for 24 h. The reaction was quenched by the addition of water (10 mL) slowly at 0 °C and then diluted with 5% aqueous HCl (20 mL). The aqueous layer was extracted with ether (3 × 50 mL). The combined organic layer was washed with $NaHCO_3$ (20 mL), dried over anhydrous and concentrated to afford **3** as a light yellow solid (2.14 g, 91.2% yield), mp = 66–68 °C [lit.[12]: 68–72 °C]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 8.5 Hz, 2H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.35–7.33 (m, 2H), 7.19–7.16 (m, 2H), 7.05 (d, *J* = 8.4, 2H), 2.02 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.1, 134.3, 132.8, 132.2, 128.8, 127.9, 127.4, 126.1, 125.6, 124.9, 20.0 ppm. $[\alpha]_D^{25}$ = −40.5 (*c* 1, CH_2Cl_2).

4.1.4. General synthetic procedures for (*R*)-2,2′-dibromomethyl-1,1′-binaphthyl 4

To a solution of (*R*)-2,2′-dimethyl-1,1′-binaphthyl (2.8 g, 10.0 mmol) in cyclohexane (60 mL) was added *N*-bromosuccinimide (3.56 g, 20.0 mmol) and benzoyl peroxide (0.24 g, 1.0 mmol). The reaction mixture was heated at reflux and irradiated under a 250 W infrared lamp for 8 h. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure. After removal of the solvent, the residue was recrystallized from EtOAc to afford **4** as a white solid (2.64 g, 60.0% yield), mp = 184–186 °C [lit.[21]: 185–187 °C]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.0 Hz, 2H), 7.92 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.46–7.44 (m, 2H), 7.25–7.23 (m, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 4.26 (s, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.2, 134.1, 133.3, 132.5, 129.4, 128.0, 127.8, 127.6, 126.8, 32.6 ppm. $[\alpha]_D^{25}$ = −89.3 (*c* 1, CH_2Cl_2).

4.2. General synthetic procedures for ligand L

A solution of **2** (2.0 mmol), **4** (0.97 g, 2.2 mmol), and triethylamine (0.44 g, 4.4 mmol) in anhydrous CH_2Cl_2 (30 ml) was heated at reflux for 24 h under Ar. The reaction was cooled to room temperature and quenched by the addition of distilled water (15 ml), and the aqueous layer was extracted with CH_2Cl_2. The combined organic phase was washed with brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography using silica gel (Hexane/EtOAc = 3/1, v/v) to give product **L**.

4.2.1. (*S*)-1-(2-((*R*)-3*H*-Dinaphtho[2,1-c:1′,2′-e]azepin-4(5*H*)-yl)ethyl)-*N*-butylpyrrolidine-2-carboxamide L1

Yellow colloidal solid (0.49 g, 50.3% yield), mp = 56–60 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 8.4 Hz, 4H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.47 (dd, *J* = 7.4, 5.8 Hz, 4H), 7.28 (d, *J* = 7.8 Hz, 2H), 3.68 (d, *J* = 12.3 Hz, 2H), 3.39 (td, *J* = 13.9, 7.1 Hz, 1H), 3.28–3.18 (m, 4H), 3.15 (dd, *J* = 10.0, 4.2 Hz, 1H), 2.98–2.85 (m, 1H), 2.81–2.66 (m, 2H), 2.52–2.34 (m, 2H), 2.29–2.10 (m, 2H), 1.98–1.87 (m, 1H), 1.84–1.66 (m, 2H), 1.52–1.42 (m, 2H), 1.34 (dq, *J* = 14.1, 7.0 Hz, 2H), 0.88 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.1, 135.1, 135.0, 133.3, 133.2, 133.1, 132.6, 131.4, 128.6, 128.4, 128.3, 128.3, 127.6, 127.5, 127.4, 126.0, 125.9, 125.7, 125.6, 68.0, 58.4, 56.5, 55.9, 55.1, 54.7, 54.4, 38.8, 31.9, 30.7, 29.7, 29.4, 24.5, 22.7, 20.2, 14.1, 13.8 ppm. ESI-MS+ *m*/*z* calcd. for $C_{33}H_{38}N_3O$ 492.3015 $[M+H]^+$; found 492.3014. $[\alpha]_D^{25}$ = −248.0 (*c* 0.5, CH_2Cl_2).

4.2.2. (*S*)-1-(2-((*R*)-3*H*-Dinaphtho[2,1-c:1′,2′-e]azepin-4(5*H*)-yl)ethyl)-*N*-(*tert*-butyl)pyrrolidine-2-carboxamide L2

Light yellow solid (0.53 g, 53.7% yield), mp = 168–170 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 8.4 Hz, 4H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.50–7.42 (m, 4H), 7.27 (d, *J* = 7.6 Hz, 2H), 3.69 (d, *J* = 12.3 Hz, 2H), 3.22 (t, *J* = 8.9 Hz, 2H), 3.05–2.88 (m, 2H), 2.78–2.62 (m, 2H), 2.52 (dd, *J* = 19.1, 9.6 Hz, 1H), 2.37 (td, *J* = 9.5, 6.6 Hz, 1H), 2.24–2.08 (m, 2H), 1.93–1.60 (m, 4H), 1.38 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.2, 135.0, 133.2, 131.4, 128.4, 128.3, 127.7, 127.5, 125.8, 125.5, 68.8, 55.9, 54.82, 54.7, 54.7, 50.2, 30.6, 29.7, 28.9, 24.3 ppm. ESI-MS+ *m*/*z* calcd. For $C_{33}H_{38}N_3O$ 492.3015 $[M+H]^+$; found 492.3025. $[\alpha]_D^{25}$ = −222.8 (*c* 0.5, CH_2Cl_2).

4.2.3. (*S*)-1-(2-((*R*)-3*H*-Dinaphtho[2,1-c:1′,2′-e]azepin-4(5*H*)-yl)ethyl)-*N*-cyclohexylpyrrolidine-2-carboxamide L3

Light yellow solid (0.57 g, 54.8% yield), mp = 82–84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99–7.88 (m, 4H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.47 (dd, *J* = 7.6, 6.5 Hz, 4H), 7.28 (dd, *J* = 7.1, 1.5 Hz, 2H), 3.83–3.73 (m, 1H), 3.70 (d, *J* = 12.3 Hz, 2H), 3.29–3.19 (m, 3H), 3.11 (dd, *J* = 10.1, 4.5 Hz, 1H), 2.94 (dt, *J* = 10.1, 7.2 Hz, 1H), 2.78–2.66 (m, 2H), 2.51 (dd, *J* = 14.6, 4.7 Hz, 1H), 2.44–2.34 (m, 1H), 2.28–2.12 (m, 2H), 2.01–1.92 (m, 1H), 1.87 (ddd, *J* = 12.6, 7.9, 3.5 Hz, 2H), 1.81–1.59 (m, 5H), 1.48–1.32 (m, 2H), 1.22–1.05 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.0, 135.0, 133.2, 133.0, 131.4, 128.4, 128.3, 127.7, 127.4, 125.9, 125.6, 68.0, 55.8, 54.8, 54.4, 47.5, 33.4, 33.1, 30.7, 25.6, 25.0, 24.9, 24.3 ppm. ESI-MS+ *m*/*z* calcd. for $C_{35}H_{40}N_3O$ 518.3171 $[M+H]^+$; found 518.3168. $[\alpha]_D^{25}$ = −229.4 (*c* 0.5, CH_2Cl_2).

4.2.4. (*S*)-1-(2-((*R*)-3*H*-Dinaphtho[2,1-c:1′,2′-e]azepin-4(5*H*)-yl)ethyl)-*N*-phenylpyrrolidine-2-carboxamide L4

Light yellow solid (0.62 g, 60.3% yield), mp = 165–168 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.01 (s, 1H), 7.92 (d, *J* = 8.1 Hz, 2H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.63 (d, *J* = 7.9 Hz, 2H), 7.44 (dd, *J* = 14.3, 7.5 Hz, 4H), 7.30 (t, *J* = 7.9 Hz, 3H), 7.24 (dd, *J* = 8.4, 1.8 Hz, 3H), 7.15 (t, *J* = 7.4 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.70 (d, *J* = 12.3 Hz, 2H), 3.33–3.19 (m, 3H), 3.04–2.90 (m, 1H), 2.48 (dt, *J* = 14.3, 7.4 Hz, 2H), 2.33–2.18 (m, 1H), 2.14–2.06 (m, 1H), 1.93–1.68 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.0, 138.1, 135.0, 133.1, 131.3, 129.0, 128.3, 128.2, 127.8, 127.4, 125.8, 125.6, 124.0, 119.9, 68.4, 60.4, 55.8, 54.8, 54.1, 30.7, 29.6, 24.6, 21.1, 14.2 ppm. ESI-MS+ *m*/*z* calcd. for $C_{35}H_{34}N_3O$ 512.2702 $[M+H]^+$; found 512.2715. $[\alpha]_D^{25}$ = −297.4 (*c* 0.5, CH_2Cl_2).

4.2.5. (*S*)-1-(2-((*R*)-3*H*-Dinaphtho[2,1-c:1′,2′-e]azepin-4(5*H*)-yl)ethyl)-*N*-(naphthalen-1-yl)pyrrolidine-2-carboxamide L5

Light yellow solid (0.65 g, 55.2% yield), mp = 200–202 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.47 (s, 1H), 8.17–8.10 (m, 1H), 7.95–7.90 (m, 2H), 7.89–7.84 (m, 2H), 7.84–7.80 (m, 1H), 7.74–7.68 (m, 1H), 7.57–7.50 (m, 1H), 7.49–7.42 (m, 4H), 7.42–7.35 (m, 3H), 7.25–7.16 (m, 3H), 7.00 (s, 1H), 3.65 (s, 2H), 3.56–3.48 (m, 1H), 3.44 (dd, *J* = 10.2, 4.0 Hz, 1H), 3.23–3.04 (m, 3H), 3.00–2.88 (m, 2H), 2.70–2.58 (m, 2H), 2.33 (ddd, *J* = 18.9, 12.9, 9.6 Hz, 1H), 2.22–2.12 (m, 1H), 1.99–1.90 (m, 2H) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7, 134.9, 134.0, 133.1, 132.7, 131.3, 128.5, 128.3, 127.7, 127.4, 126.4, 125.9, 125.8, 125.6, 125.5, 124.6, 120.5, 118.5, 68.9, 55.8, 55.0, 54.7, 54.3, 31.0, 24.9 ppm. ESI-MS+ *m*/*z* calcd. for $C_{39}H_{36}N_3O$ 562.2858 $[M+H]^+$; found 562.2819. $[\alpha]_D^{31}$ = +239.0 (*c* 0.5, CH_2Cl_2).

4.2.6. (*R*)-4-(2-(Pyrrolidin-1-yl)ethyl)-4,5-dihydro-3*H*-dinaphtho[2,1-c:1′,2′-e]azepine L6

To a solution of pyrrolidine (15.0 mmol) in CH_3CN (60 mL) was added K_2CO_3 (3.10 g, 22.5 mmol) and *N*-Cbz-2-bromoethylamine (3.87 g, 15.0 mmol) under stirring and kept at 80 °C, and monitored by TLC (Hexane/EtOAc = 2/1, v/v), after which K_2CO_3 was removed by filtration. The filtrate was concentrated to give a light brown oil. The oil was dissolved in ethyl acetate (150 mL) and the solution was washed with water (2 × 50 mL). The organic phase was dried

over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude product benzyl (2-(pyrrolidin-1-yl)ethyl)carbamate (2.54 g, 68.3% yield) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.34 (m, 4H), 7.34–7.28 (m, 1H), 5.09 (s, 2H), 3.40–3.19 (m, 2H), 2.58 (t, J = 6.0 Hz, 2H), 2.49 (s, 4H), 1.77–1.73 (m, 4H), 1.26 (t, J = 7.1 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.5, 136.7, 128.5, 128.2, 128.1, 66.6, 60.4, 54.9, 53.8, 39.7, 23.5, 21.1 ppm. ESI-MS+ m/z calcd. for $C_{14}H_{21}N_2O_2$ 249.1603 [M+H]$^+$; found 249.1580. $[\alpha]_D^{31}$ = −79.4 (c 0.51, CH_2Cl_2).

To a 50 mL three-necked flask was added the above compound (1.24 g), and then dissolved in anhydrous MeOH (30 mL), after which 0.05 g Pd/C (10%, w/w) were added to the solution. The mixture was stirred at room temperature for 4 h under a hydrogen atmosphere. The reaction solution was filtered and the filtrate was concentrated under reduced pressure to afford a light yellow oil 2-(pyrrolidin-1-yl)ethanamine. This compound was used directly in the next step.

A solution of 2-(pyrrolidin-1-yl)ethanamine (0.23 g), **4** (0.97 g, 2.2 mmol), and triethylamine (0.44 g, 4.4 mmol) in anhydrous CH_2Cl_2 (30 mL) was heated at reflux for 24 h under Ar. The reaction was cooled to room temperature and quenched by the addition of distilled water (15 mL). The aqueous layer was extracted with CH_2Cl_2. The combined organic phase was washed with brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography using silica gel (Hexane/CH_3OH = 10/1, v/v) to give the product **L6** as a light yellow solid (0.24 g, 41.6% yield), mp = 230–234 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (dd, J = 8.0, 5.6 Hz, 4H), 7.60 (d, J = 8.3 Hz, 2H), 7.50–7.42 (m, 4H), 7.29 (d, J = 1.1 Hz, 1H), 7.25 (d, J = 1.1 Hz, 1H), 4.21 (s, 4H), 3.78 (d, J = 12.3 Hz, 2H), 3.29–3.20 (m, 6H), 2.07 (t, J = 6.6 Hz, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.1, 133.3, 132.4, 131.4, 128.7, 128.4, 127.6, 127.4, 126.0, 125.7, 55.3, 54.3, 53.1, 51.3, 29.7, 23.3 ppm. ESI-MS+ m/z calcd. for $C_{28}H_{29}N_2$ 393.2331 [M+H]$^+$; found 393.2326. $[\alpha]_D^{25}$ = +63.7 (c 0.19, CH_2Cl_2).

4.2.7. (*S*)-1-(2-(Isoindolin-2-yl)ethyl)-*N*-(naphthalen-1-yl) pyrrolidine-2-carboxamide L7

A solution of **2e** (2.0 mmol), 1,2-bis(bromomethyl)benzene (0.97 g, 2.2 mmol), and triethylamine (0.44 g, 4.4 mmol) in anhydrous CH_2Cl_2 (30 mL) was refluxed for 24 h under Ar. The reaction was cooled to room temperature and quenched by the addition of distilled water (15 mL). The aqueous layer was extracted with CH_2Cl_2. The combined organic phase was washed with brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography using silica gel (Hexane/EtOAc = 4/1, v/v) to give product **L7** (0.61 g, 43.5% yield), mp = 70–74 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.78 (s, 1H), 8.28 (dd, J = 7.5, 0.6 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.2 Hz, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.41 (t, J = 7.9 Hz, 1H), 7.24–7.21 (m, 1H), 7.03–6.91 (m, 3H), 6.90–6.81 (m, 2H), 3.89 (d, J = 10.9 Hz, 2H), 3.77 (d, J = 10.9 Hz, 2H), 3.52–3.38 (m, 2H), 3.04–2.87 (m, 4H), 2.62 (ddd, J = 15.8, 9.0, 7.2 Hz, 1H), 2.38–2.24 (m, 1H), 2.21–2.11 (m, 1H), 1.88 (tt, J = 8.9, 4.9 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8, 139.5, 133.8, 132.9, 128.1, 126.4, 125.9, 125.6, 125.5, 124.3, 121.8, 120.4, 117.4, 68.6, 59.0, 55.1, 31.0, 24.8 ppm. ESI-MS+ m/z calcd. for $C_{25}H_{28}N_3O$ 386.2232 [M+H]$^+$; found 386.2230. $[\alpha]_D^{31}$ = −79.4 (c 0.51, CH_2Cl_2).

4.3. General procedure for the asymmetric Henry reaction

A mixture of ligand **L5** (28 mg, 0.05 mmol, 10 mol %) and Cu $(OAc)_2$ (9 mg, 0.05 mmol, 10 mol %) was stirred in EtOH (1 mL) at room temperature for 30 min to form the complex catalyst. Then nitroalkane (5 mmol) was added to the mixture. After the addition, the resulting mixture was cooled to 10 °C and the corresponding aldehyde (0.5 mmol) was added. The reaction mixture was stirred at 10 °C until the reaction was decided to be complete based on TLC (Hexane/EtOAc = 3/1, v/v) analysis. The reaction mixture was directly purified by column chromatography on silica gel eluted to afford the nitroaldol product **6**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2016.05.005.

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