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PII: S0040-4020(19)30819-1

DOI: https://doi.org/10.1016/j.tet.2019.130492

Reference: TET 130492

To appear in: *Tetrahedron*

Received Date: 14 May 2019

Revised Date: 17 July 2019

Accepted Date: 27 July 2019

Please cite this article as: Gao E, Li M, Duan L, Li L, Li Y-M, Isosteric expansion of the structural diversity of chiral ligands: Design and application of proline-based *N,N′*-dioxide ligands for copper-catalyzed enantioselective Henry reactions, *Tetrahedron* (2019), doi: https://doi.org/10.1016/j.tet.2019.130492.

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En Gao, Meng Li, Lili Duan, Lin Li* and Yue-Ming Li*

State Key Laboratory of Medicinal Chemical Biology, College of Pharmacy and Tianjin Key Laboratory of Molecular Drug Research, Nankai University, Tianjin, People's Republic of China.

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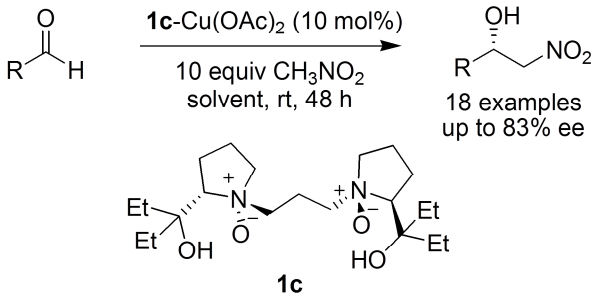

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Isosteric Expansion of the Structural Diversity of Chiral Ligands: Design and Application of Proline-Based *N,N′*-Dioxide Ligands for Copper-Catalyzed Enantioselective Henry Reactions

En Gao,[a] Meng Li,[a] Lili Duan,[a] Lin Li[a*] and Yue-Ming Li[a,b*]

[a]*State Key Laboratory of Medicinal Chemical Biology, College of Pharmacy and Tianjin Key Laboratory of Molecular Drug Research, Nankai University, Tianjin, People's Republic of China.*
[b]*Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, People's Republic of China.*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
asymmetric catalysis
chiral *N,N′*-dioxide ligand
copper(II) complex
Henry reaction
proline

ABSTRACT

Chiral *N,N′*-dioxide catalysts were designed based on isosteric approach. Using L-Proline as the starting material, a variety of chiral *N,N′*-dioxide ligands were obtained via conventional functional group transformations and were utilized in asymmetric Henry reactions between nitromethane and aromatic aldehydes. Using the *N,N′*-dioxide-copper(II) complexes as the catalysts, asymmetric Henry reaction produced the corresponding β-nitroalcohols in up to 66% yields and up to 83% ee's under mild conditions. The reactions were easy to carry out, and special care such as air or moisture-free conditions was not required.

1. Introduction

Chiral ligand design remains the focal point of asymmetric catalysis, and significant efforts have been made for the design and synthesis of chiral ligands for different asymmetric reactions.[1] As a result, numerous chiral ligands have been prepared from easily available starting structures.[2] Among the various chiral ligands developed, L-proline-based chiral ligands have shown great potential due to the unique structure feature, the easy availability of the starting material and the outstanding performance of the chiral catalysts in asymmetric organic reactions.[3]

Proline-promoted asymmetric transformation can be dated back to 1970s.[4] It was well recognized as starting materials for chiral auxiliaries in alkylation of carbonyl compounds[5] and for chiral ligands/catalysts in enantioselective reduction of prochiral ketones.[6] So far, many chiral ligands have been developed using proline or hydroxyproline as the starting structures, and have been successfully applied in a variety of asymmetric organic reactions (Figure 1).[7] Among these studies, chiral ligands developed by Feng et al. have received significant success due to the excellent performance of these *N,N′*-dioxide-type chiral ligands in a large variety of asymmetric catalytic reactions.[8] The early achievements could be exemplified by asymmetric cyanosilylation of ketones[9] as well as asymmetric Strecker reactions.[10]

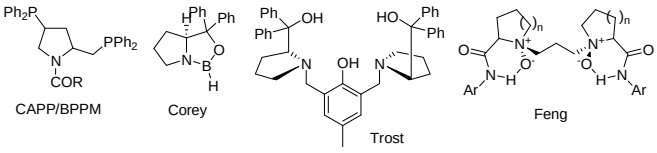


Figure 1. Examples of Chiral Ligands Developed from Proline and Related Compounds.

It is our purpose to expand the structural diversity of these chiral ligands. Herein, we wish to present our preliminary results of isosteric approach to expanding the structural diversity of proline-based chiral ligands, and the application of these chiral ligands in asymmetric Henry reactions.

2. Results and discussion

Feng et al. have shown that *N,N′*-dioxides are viable chiral ligands in a variety of asymmetric reactions. The two *N*-oxide functional groups were formed via *N*-oxidation of either proline or pipecolinic acid, and acted as the main coordination atoms in a variety of chiral catalysts. The catalytic activity of these chiral catalysts came from the two *N*-oxide atoms as well as the adjacent amide functional groups which could interact with the two oxygen atoms via intramolecular hydrogen bonding. The stereoelectronic property of the chiral ligand/catalyst could be further regulated by changing the structure of aryl groups (Figure 2).

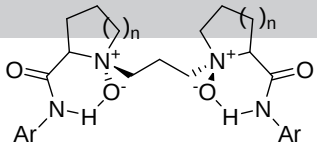
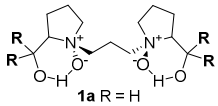


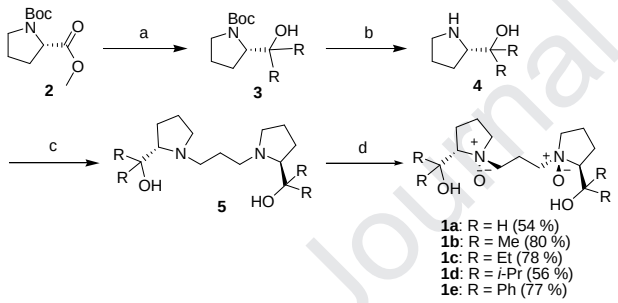
Figure 2. Example of Feng's ligand.

Inspired by these rationales, we decided to expand the structure diversity of these *N*,*N*′-dioxide chiral ligands using isosteric approach. The concept of isostere or bioisotere was originally formulated by Moir and refined by Langmuir,[11] and has been used as a general method in drug design and discovery.[12] Keeping this idea in mind, chiral ligands **1a**-**1e** were designed by replacing two carboxamide functional groups with alcohol moieties. Tertiary alcohols were adopted to avoid the introduction of additional chiral centers.



1a R = H
1b R = Me
1c R = Et
1d R = *i*-Pr
1e R = Ph

The preparation of these chiral ligands started from *N*-protected methyl prolinate. Reduction of the ester functional group provided prolinol **3a** (R = H). Reactions of *N*-Boc methyl prolinate **2** with different Grignard reagents gave the corresponding prolinols **3b**-**3e**. Removal of the protective groups produced prolinols **4**, and subsequent reactions of **4** with 1,3-dibromopropane gave compounds **5**. The desired chiral ligands **1a**-**1e** were obtained after *N*-oxidation of the prolinol dimers **5** with *m*-CPBA.



1a: R = H (54 %)
1b: R = Me (80 %)
1c: R = Et (78 %)
1d: R = *i*-Pr (56 %)
1e: R = Ph (77 %)

Reaction conditions: a) 3a: $LiAlH_4$ (1 equiv), 80%. 3b: MeMgBr (4.5 equiv), 75%. 3c: EtMgBr (4.5 equiv), 58%. 3d: i-PrMgBr (4.5 equiv), 55%. 3e: C_6H_5MgBr (4.5 equiv), 86%. b) TFA (10 equiv), 4a: 90%. 4b: 92%. 4c: 94%. 4d: 93%. 4e: 91%. c) 1,3-dibromopropane (0.5 equiv). 5a: R = H, 54%. 5b: R = Me, 93%. 5c: R = Et, 90%. 5d: R = i-Pr, 85%. 5e: R = Ph, 89%. d) m-CPBA (2.2 equiv). 1a: 54%. 1b: 80%. 1c: 78%. 1d: 56%. 1e: 77%.

Scheme 1. Synthesis of Chiral *N*,*N*′-dioxides **1a**-**1e.**

To further prove the stereochemistry of *N*-oxide, ligands **1c** and **1e** were carefully crystalized and subjected to X-ray diffraction experiments. ORTEP drawing of these ligands indicated the presence of intramolecular hydrogen bonds between hydroxyl groups and the oxygen atoms of the *N*-oxide, and clearly confirmed the absolute configurations of the nitrogen atoms (Figure 3).[13]

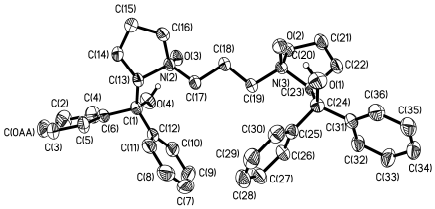
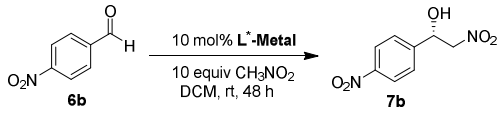


Figure 3. ORTEP Drawing of compound **1e** at 30% displacement ellipsoid probability (the hydrogen atoms and the co-crystalized CH_2Cl_2 are omitted for clarity).

After the preparation of the chiral ligands, copper(II) complex-catalyzed asymmetric Henry reaction was carried out as model reaction to prove the isosteric concept and to evaluate the performance of these chiral ligands. The Henry (nitroaldol) reaction is a versatile C-C bond-forming reaction, and has been proved as a useful method for the construction of different nitroolefins, nitro carbonyl compounds and 1,2-amino alcohols.[14] So far, different chiral catalysts have been developed for this purpose, and chiral *N*,*N*′-dioxide-based chiral catalysts have been successfully applied in asymmetric Henry[15] and aza-Henry reactions.[16]

Thus, copper(II) complex-catalyzed asymmetric Henry reaction of nitromethane with *p*-nitrobenzaldehyde was carried out at 35 °C using chiral *N*,*N*′-dioxide **1a**-**1e** as chiral ligands. The copper salts were used based on literature studies on asymmetric Henry reactions. The results are summarized in Table 1.

Table 1. Screening of Copper Salts and Chiral Ligands in Asymmetric Henry Reactions[a]



6b **7b**

Entry	Ligand[b]	Copper source	Yield (%)[c]	ee (%)[de]
1	**1a**	$Cu(OAc)_2$	33%	0
2	**1b**	$Cu(OAc)_2$	32%	45%
3	**1c**	$Cu(OAc)_2$	38%	60%
4	**1d**	$Cu(OAc)_2$	25%	56%
5	**1e**	$Cu(OAc)_2$	12%	0
6	**1c**	CuF_2	22%	19%
7	**1c**	$CuBr_2$	11%	4.1%
8	**1c**	CuCl	34%	0
9	**1c**	$Cu(NO_3)_2$	38%	0
10	**1c**	$CuSO_4$	ND	--
11	**1c**	CuOTf	ND	--
12	**1c**	$Cu(OTf)_2$	ND	--
13[f]	**1c**	$Cu(OAc)_2$	30%	50%
14[g]	**1c**	$Cu(OAc)_2$	36%	55%
15	**5c**	$Cu(OAc)_2$	37%	35%
16	**1c'**	$Cu(OAc)_2$	41%	0
17	**1c"**	$Cu(OAc)_2$	39%	0

Reaction conditions:

[a]Reactions were carried out in 0.1 mmol scale of *p*-nitrobenzaldehyde in 2.5 mL of DCM; ligand-to-metal ration= 1:1 (10 mol %); nitromethane (10 equiv).

[b]Structure identity of all ligands were determined by 1H NMR, 13C NMR and HRMS.

[c]Isolated yields.

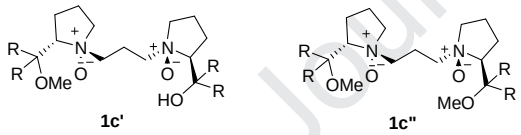
[d]Determined by HPLC on a Chiralcel OD-H column.

[e]The configurations was S, determined by comparison of the optical rotation with reported results in the literature.[17]

[f]Ligand-to-$Cu(OAc)_2$ ratio = 1:2 (10 mol %).

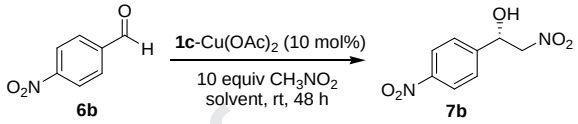
[g]Ligand-to-$Cu(OAc)_2$ ratio = 1.25:1 (10 mol %).

As shown in Table 1, different results were obtained when combination of $Cu(OAc)_2$ and different chiral ligands were used to promote the reactions. Catalyst with ligand **1a** was able to promote the reaction but showed no enantioselectivity, possibly due to the unfavorable steric feature of the ligand. Gradually increasing the steric hindrance of the chiral ligands by introducing substituents into the hydroxymethyl group led to the increase of the enantioselectivity, and chiral ligand **1c** gave the most promising result in the reactions. Further increasing the steric hindrance of the ligands led to drops of the enantioselectivity. Combination of **1c** with $CuBr_2$, CuCl or $Cu(NO_3)_2$ was able to promote the reactions, but no stereoselectivity was observed, possibly due to the background reactions induced by the uncoordinated salts (Table 1, entries 7-9). No desired product was observed when $Cu(OTf)_2$, CuOTf or $CuSO_4$ was used as the copper source, possibly due to the poor solubility of these salts in the reaction medium (Table 1, entries 10-12). Lower ee also observed when excess amount of $Cu(OAc)_2$ was used in the reaction, and the metal-to-ligand ratio was finally fixed to 1:1. Lower ee was observed when compound **5c** was subjected to the model reaction, suggesting the important role of the *N*-oxide functionality. Methylation of one or two hydroxyl groups in **1c** gave ligands **1c'** and **1c".** Drops of enantioselectivity were observed when these ligands were subjected to the same reaction under otherwise identical conditions, indicating the stereoelectronic demand of the ligands.



After the proof of the concept of the isosteric approach to the design of chiral ligands, reactions in different solvents were further carried out to get the most suitable media for the reactions. A series of solvents such as chloroform, toluene, THF were screened (Table 2, entries 1-8). Toluene and isopropanol gave moderate yields and ee values (Table 2, entries 2 and 5). Ether solvents were found to be superior to other solvents in terms of the yields (Table 2, entries 3 and 6). Reaction in 1,4-dioxane gave product in highest isolated yield (Table 2, entry 6), and highest ee value was observed when reaction was carried out in chloroform (Table 2, entry 1). The reaction was then carried out in a mixture of chloroform and dioxane in an attempt to increase both the yield and the ee, and the ratio of chloroform to dioxane was finally fixed to 4:1 after careful screening of the reaction conditions. Both the yield and the enantioselectivity were dramatically influenced by catalyst loading, and the most favorable catalyst loading was found to be 10 mol%. The effect of additive also showed some impact on the reactions, and both the yield and stereoselectivity were enhanced upon addition of molecular sieve (4 Å MS) (Table 2, entry 13). Temperature also showed some impact on the reaction, and the reaction temperature was finally fixed at 25 °C (Table 2, entry 14). Increasing the temperature caused a drop in enantioselectivity (Table 2, entry 15), and further lowering the temperature led to a dramatic decrease in reactivity without any improvement in enantioselectivity (Table 2, entry 16-17). The effect of air and moisture on the enantioselectivity of the Henry reaction was also studied. The reaction was not sensitive to the air, and the results in argon atmosphere were almost identical to that carried out in open air. Therefore, the reactions was carried out without special care of air. After the optimization of the reaction conditions, the reaction was finally carried out in the presence of 10 mol% **1c**-$Cu(OAc)_2$ (1:1), 10 equivalents nitromethane in 3 mL of mixed solvents (chloroform : dioxane = 4:1) in the presence of 4 Å MS (20 mg) at 25 °C (Table 2, entry 14).

Table 2. Optimization of the Addition of nitromethane to p-nitrobenzaldehyde in the Presence of Cu(II)-**1c** Complex[a]



Entry	**1c** (mol%)	Solvent	Temp (°C)	Yield (%)[b]	ee (%)[c]
1	10	$CHCl_3$	35	25	68
2	10	toluene	35	30	38
3	10	THF	35	36	60
4	10	MeCN	35	21	0
5	10	*i*-PrOH	35	22	37
6	10	dioxane	35	65	43
7	10	chlorobenzene	35	19	53
8	10	DCE	35	12	52
9[d]	10	4:1	25	54	70
10[d]	10	3:2	35	57	60
11	15	$CHCl_3$	35	35	63
12	20	$CHCl_3$	35	40	62
13[d,e]	10	4:1	35	56	72
14[d,e]	10	4:1	25	55	79
15[d,e]	10	4:1	45	60	55
16[d,e]	10	4:1	0	45	78
17[d,e]	10	4:1	-10	25	77

Reaction conditions: [a]Unless otherwise specified, reactions were carried out on a 0.25 mmol scale of *p*-nitrobenzaldehyde in 3.0 mL of solvent; nitromethane (10 equiv); ligand-to-$Cu(OAc)_2$ ratio = 1:1 (10 mol %). Reaction time = 48 h.

[b]Isolated yield.

[c]Determined by HPLC on a Chiralcel OD-H column.

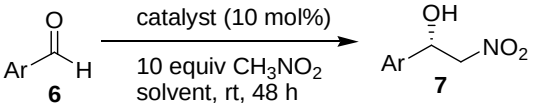
[d]Ratio of $CHCl_3$-to-dioxane.

[e]In the presence of 4 Å MS (20 mg).

After optimization of the reaction conditions, the scope of the catalytic enantioselective Henry reaction was then investigated by reacting various aldehydes with nitromethane. The results are summarized in Table 3. As these results showed, asymmetric Henry reaction of aromatic aldehydes proceeded smoothly, providing the corresponding nitroalcohols in high yields and moderate to good enantioselectivities (Table 3). Both electron-rich or electron-deficient aromatic aldehydes were found to be good substrates for this reaction. Aromatic aldehydes bearing electron-withdrawing nitro groups gave results better than from substrates bearing the electron-donating groups (Table 3, entries

2-8). Substrates **6d** and **6h** with the ortho substituents gave higher ee (80% ee and 83% ee, Table 3, entries 4 and 8) possibly due to larger steric hindrance of the ortho substituent in the substrates. Even with the bulker aldehydes such as 2-naphthaldehyde, the reactivity and enantioselectivity were still maintained (68% ee and 45% yield, Table 3, entries 17). Reactions of heteroaromatic aldehydes were less successful, possibly due to the coordination of heteroatom with the catalyst. The absolute configurations were assigned to be S based on previous reports.[17]

Table 3. Asymmetric Henry reactions between nitromethane and various aldehydes



Entry	Aldehydes	Yield (%)[bc]	ee (%)[cd]	Config[e]
1	benzaldehyde (**6a**)	40 (95)	40 (95)	(S)
2	4-nitrobenzaldehyde (**6b**)	66 (99)	77 (85)	(S)
3	3-nitrobenzaldehyde (**6c**)	55 (99)	82 (85)	(S)
4	2-nitrobenzaldehyde (**6d**)	63 (81)	80 (73)	(S)
5	4-fluorobenzaldehyde (**6e**)	56	60	(S)
6	3-fluorobenzaldehyde (**6f**)	58	66	(S)
7	4-chlorobenzaldehyde (**6g**)	50 (99)	55 (86)	(S)
8	2-chlorobenzaldehyde (**6h**)	58	83	(S)
9	4-bromobenzaldehyde (**6i**)	56	63	(S)
10	2-bromobenzaldehyde (**6j**)	61	76	(S)
11	4-methoxybenzaldehyde (**6k**)	32	60	(S)
12	3-methoxybenzaldehyde (**6l**)	35 (99)	65 (95)	(S)
13	2-methoxybenzaldehyde (**6m**)	48	71	(S)
14	4-methylbenzaldehyde (**6n**)	40 (44)	46 (91)	(S)
15	3-methylbenzaldehyde (**6o**)	32 (87)	60 (93)	(S)
16	3,4-dimethylbenzaldehyde (**6p**)	30	59	(S)
17	2-naphthaldehyde (**6q**)	45 (88)	68 (95)	(S)
18	2-thiophenaldehyde (**6r**)	30 (80)	35 (95)	(S)

Reaction conditions:

[a]All the reaction were carried out with 0.1 mmol p-nitrobenzaldehyde and 1.0 mmol nitromethane in 3.0 mL of mixed solvents (chloroform : dioxane = 4:1) in the presence of 10 mol % $Cu(OAc)_2$ and 10 mol % ligand.

[b]Isolated yield.

[c]Data in parentheses are results from Feng's work. (Ref. 18)

[d]Determined by HPLC analysis on a chiralcel OD-H or AD-H column.

[e]By comparison with the literature data.

A side-by-side comparison with Feng's catalyst system indicated that the current catalysts system compared unfavorably with Feng's catalyst (Table 3, entries 1-4,7,12,14-15,17 and 18).[18] To get structural insights into the current catalyst system, computation on Cu(II)-**1c** was carried out with 6-31G(d,p)[19] basis set at ωB97XD[20] level of theory using Gaussian 09 D01 package.[21] Preliminary result was shown in Figure 4.

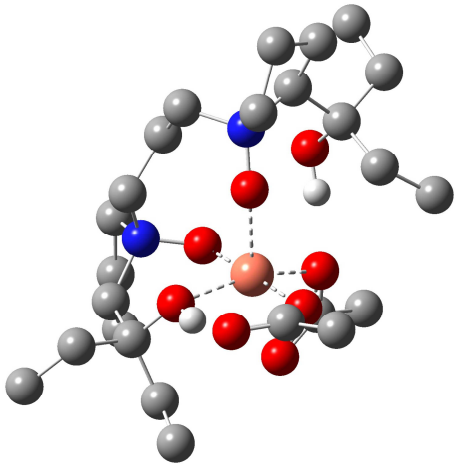


Figure 4. Computed model of catalyst $Cu(OAc)_2$-**1c**.

This preliminary model indicated that the central metal adopted a distorted square pyramidal structure, and was highly crowded comparing to Feng's catalyst.[18] The aldehyde approached the catalyst from the axial position opposite to one of the N-oxide oxygen atom with Si-face exposing to nucleophilic attack (Figure 5). Due to the highly hindered nature of the central metal, the approaching of the substrate to the metal was less effective comparing to Feng's catalyst, thus causing the low activity of the catalyst system.

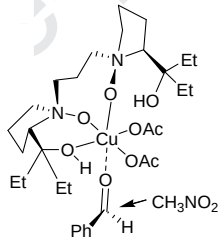


Figure 5. Proposed working model for the Henry reaction of aldehyde with nitro-methane.

3. Conclusion

In summary, new chiral *N,N'*-dioxide ligands were designed based on isosteric approach and have been used in Cu(II)-catalyzed asymmetric Henry reactions. A computation model on the catalyst indicated that the central metal was sterically hindered, and rendering the catalyst system less efficient as compared with the original N,N'-dioxide catalyst systems. Further study focusing on tackling the problem of stereoselectivity by replacing copper with different metals was carrying out in the group, and the results will be reported in due time.

4. Experimental Section

4.1 General Experimental Information

All reactions were carried out with commercially available reagents in oven-dried apparatus. Thin layer chromatography (TLC) was performed on silica gel GF_{254}. Column chromatography was performed employing 200-300 mesh silica gel unless otherwise noted. Melting points were measured on a digital melting-point apparatus without correction of the thermometer. ^1H and ^{13}C NMR spectra were recorded at 298 K using deuterated chloroform as solvent and TMS as internal reference. Infrared spectra were reported in wave number (cm^{-1}). HRMS analyses were carried out with Varian FTICR-MS 7.0T. The enantiomeric excesses were determined by HPLC analysis

on chiral DAICEL CHIRALCEL OD-H or CHIRALPAK AD-H column. Optical rotations are measured on a commercial polarimeter and are reported as follows: $[\alpha]_D^T$ (c = g/100 mL, solvent). Unless otherwise indicated, starting materials and reagents used in the study were purchased and were used as received without further purification.

4.2. Typical Procedure for the preparation of chiral ligands **1a**-**1e**.[22]

Amino alcohol **4b** (1.07 g, 8.3 mmol) was added to a 100 mL round-bottomed flask containing 50 mL acetonitrile, then 1,3-dibromopropane (0.83 g, 4.2 mmol) and potassium carbonate (3.50 g, 2.5 mmol) was slowly added portionwise to the flask over 10 min. The mixture was stirred overnight at 95 °C, then cooled to room temperature. The solvent was removed in vacuo, water (20 mL) was added to the residue, and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic phase was dried over Na_2SO_4, filtered and concentrated. The obtained amino alcohol **5b** was used without further purification.

To a solution of amino alcohol **5b** (0.95 g, 3.2 mmol) in 15 mL dichloromethane, was added *m*-chloroperoxybenzoic acid (1.61 g, 7.0 mmol). The mixture was stirred at room temperature for 12 h, and the solvent was removed in vacuo to give the crude product. Compound **1b** was obtained in 80% (1.02 g) after column chromatography through silica gel (ethyl acetate as eluent).

*4.2.1. (1R,1'R,2S,2'S)-1,1'-(propane-1,3-diyl)bis(2-(2-hydroxypropan-2-yl)pyrrolidine 1-oxide) (**1b**).*

Compound **1b** was prepared according to the general procedure and was isolated as brown solid; mp: 130-138 °C; $[\alpha]_D^{20}$ = -43.99 (c = 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, Chloroform-d, 25 °C, TMS): δ= 8.70 (s, 2H), 3.98-3.68 (m, 2H), 3.63-3.32 (m, 6H), 3.24 (t, *J* = 8.7 Hz, 2H), 2.62 (t, *J* = 7.3 Hz, 2H), 2.53-2.39 (m, 2H),2.33-2.19 (m, 2H), 2.13-1.98 (m, 2H), 1.95-1.76 (m, 2H), 1.50 (s, 6H), 1.23 (s, 6H). ^{13}C NMR(101 MHz, $CDCl_3$) δ 80.9, 71.2, 69.5, 67.7, 29.9, 28.2, 25.6, 21.3, 20.0. IR (KBr): υ = 3433, 2974, 1480, 1362, 962, 652 cm^{-1}. HRMS (ESI, M+H$^+$) calcd. for $C_{17}H_{34}N_2O_4$ 331.2591; found 331.2595.

*4.2.2. (1R,1'R,2S,2'S)-1,1'-(propane-1,3-diyl)bis(2-(hydroxymethyl)pyrrolidine 1-oxide) (**1a**)*

Compound **1a** was prepared according to the general procedure and was isolated as brown oil (54% yield) after flash chromatography. brown oil; $[\alpha]_D^{20}$ = -2.36 ; (c =0.1, MeOH); ^{1}H NMR (400 MHz, Chloroform-d, 25 °C, TMS): δ = 4.17 (d, *J* = 13.1 Hz, 2H), 3.87 (dd, *J* = 13.1, 4.4 Hz, 2H), 3.82-3.72 (m, 2H), 3.60-3.46 (m, 4H), 3.43-3.26 (m, 4H), 2.74-2.60(m, 2H), 2.58-2.45 (m, 2H), 2.40-2.27 (m, 2H), 2.12-1.89 (m, 6H)ppm. ^{13}C NMR (101 MHz, DMSO) δ 74.7, 66.6, 63.2, 58.8, 8.7, 23.8, 20.2, 19.6. IR (KBr): υ = 3392, 2958, 1452, 1055, 734, 652 cm^{-1}. HRMS (ESI, M+H$^+$) calcd. for $C_{13}H_{26}N_2O_4$ 275.1965; found 275.1970.

*4.2.3. (1R,2S)-2-(3-hydroxypentan-3-yl)-1-(3-((1R,2S)-2-(3-hydroxypentan-3-yl)-1-oxidopyrrolidin-1-yl)propyl)pyrrolidine 1-oxide) (**1c**)*

Compound **1c** was prepared according to the general procedure and was isolated as brown solid (78% yield) after flash chromatography. mp: 165-168 °C; $[\alpha]_D^{20}$ = -27.86 (c = 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, Chloroform-d, 25 °C, TMS): δ= 8.53 (s, 2H), 3.86-3.68 (m, 2H), 3.55-3.44 (m, 2H), 3.40 (dd, *J* = 7.9, 6.1 Hz, 4H), 3.26 (t, *J* = 8.8 Hz, 1H), 2.63-2.46 (m, 4H), 2.31-2.17 (m, 2H), 2.15-2.03 (m, 2H), 2.02-1.89 (m, 2H), 1.86-1.73 (m, 4H), 1.70-1.57 (m, 2H), 1.37-1.25 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 6H), 0.78 (t, *J* = 7.5 Hz,6H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 78.6, 75.7,70.3, 68.2, 28.9, 28.7, 25.1, 21.4, 20.3, 8.0, 7.2. IR (KBr): υ = 3673, 2968, 1487, 1462, 1143, 977 cm^{-1}. HRMS (ESI, M+H$^+$) calcd. for $C_{21}H_{42}N_2O_4$, 387.3217; found 387.3220.

*4.2.4. (1R,2S)-2-(3-hydroxy-2,4-dimethylpentan-3-yl)-1-(3-((1R,2S)-2-(3-hydroxy-2,4-dimethylpentan-3-yl)-1-oxidopyrrolidin-1-yl)propyl)pyrrolidine 1-oxide (**1d**)*

Compound **1d** was prepared according to the general procedure and was isolated as brown oil (56% yield) after flash chromatography. $[\alpha]_D^{20}$ = -8.00 (c = 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, Chloroform-d, 25 °C, TMS): δ=3.89 (dt, *J* = 13.9, 7.6 Hz, 2H), 3.54-3.26 (m, 8H), 2.62-2.53 (m, 2H), 2.46-2.22 (m, 7H), 2.05-1.72 (m, 7H), 1.10 (d, *J* = 6.6 Hz, 6H), 1.01 (d, *J* = 6.9 Hz, 6H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR(101 MHz, $CDCl_3$) δ 78.7, 76.5, 69.7,68.2, 34.3, 32.4, 27.6, 22.5, 20.2, 19.3, 18.2, 17.9, 16.8. IR (KBr): υ = 3394, 2964, 1469, 1367, 1068, 942 cm^{-1}. HRMS (ESI, M+H$^+$) calcd. for $C_{25}H_{50}N_2O_4$, 343.3843; found 343.3843.

*4.2.5. (1R,2S)-2-(hydroxydiphenylmethyl)-1-(3-((1R,2S)-2-(hydroxydiphenylmethyl)-1-oxidopyrrolidin-1-yl)propyl)pyrrolidine 1-oxide (**1e**)*

Compound **1e** was prepared according to the general procedure and was isolated as brown solid (77% yield) after flash chromatography. mp: 212-216 °C; $[\alpha]_D^{20}$ = 22.00 (c = 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, Chloroform-d, 25 °C, TMS): δ= 11.36 (s, 2H), 7.71-7.61 (m, 4H), 7.56-7.43 (m, 4H), 7.33-7.22 (m, 10H), 7.18-7.09 (m, 2H), 4.22 (t, *J* = 9.0 Hz, 2H), 3.34 (t, *J* = 9.2 Hz, 2H), 3.23-3.08 (m, 2H), 2.55-2.17 (m, 7H), 2.17-2.03 (m, 2H), 2.00-1.86 (m, 2H), 1.86-1.77 (m, 2H), 1.77-1.65 (m, 1H). ^{13}C NMR (101 MHz, CDCl3) δ 147.3, 146.6, 128.2, 128.2, 126.8, 126.6, 125.9, 124.6, 77.8, 77.6, 68.7, 66.0, 26.1, 19.8, 19.5. IR (KBr): υ = 3743, 2958, 1534, 1490, 689, 657 cm^{-1}. HRMS (ESI, M+H$^+$) calcd. for $C_{37}H_{42}N_2O_4$, 579.3217; found 579.3213.

Crystal data for **1e**: $C_{37}H_{42}N_2O_4$, *M* = 578.72, *a* = 9.0796(2) ? *b* = 10.8989(2) Å *c* = 15.9762(3) ? *α* = 90°, *β* = 92.534(2)°, *γ* = 90°, *V* = 1579.42(5) Å^3, *T* = 298.80(10) K, space group *P*1211, *Z* = 2, *μ*(CuKα) = 0.622 mm^{-1}, 8675 reflections measured, 4667 independent reflections (R_{int} = 0.0150). The final R_1 values were 0.0355 ($I > 2\sigma(I)$). The final $wR(F^2)$ values were 0.0961 ($I > 2\sigma(I)$). The final R_1 values were 0.0371 (all data). The final $wR(F^2)$ values were 0.0980 (all data). The goodness of fit on F^2 was 1.007. Flack parameter = -0.04(10). CCDC 1911346.

4.3. General procedure for asymmetric Henry reaction.

A mixture of Ligand **1c** (3.86 mg, 0.01 mmol, 10 mol%), $Cu(OAc)_2$ (1.8 mg, 0.01 mmol, 10 mol%) and 4 Å molecular sieves (20 mg) was stirred in anhydrous chloroform and dioxane (2.4/0.6 mL) at room temperature for 20 min to allow the formation of the complex. Then nitromethane (61 mg, 1.0 mmol) was added to the mixture. Nitrobenzaldehyde **6b** (0.1 mmol) was then added and the mixture was stirred for 48 h. The reaction mixture was purified by column chromatography through silica gel (petroleum ether/ethyl acetate = 8:1) to afford the nitroaldol product **7b** (11.8 mg, 66% yield) as a colourless oil. Chiralcel OD-H hexane/i-PrOH. 85:15, 1.0 mL/min, *R* : t_r(minor) = 15.9 min, *S*: t_r(major) = 19.9 min; ^{1}H NMR (400 MHz, Chloroform-d, TMS): δ= 8.33-8.22 (m, 2H), 7.67-7.61 (m, 2H), 5.67-5.55 (m, 1H), 4.64-4.53 (m, 2H), 3.17 (s, 1H) ppm.

5. Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2018.XX.XXX.

Acknowledgments

We acknowledge the financial support from the National Natural Science Foundation of China (NSFC 21672106 and NSFC 21272121) and the Ministry of Tianjin Municipal Commission of Science and Technology (15JCZDJC33300). En Gao acknowledges the support from Nankai University Ph.D. Students Innovative Research Program.

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