Tetrahedron: *Asymmetry* 22 (2011) 1156–1160

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Asymmetric Henry reaction catalyzed by a Zn–amino alcohol system

Bing Zheng, Min Wang, Zhiyuan Li, Qinghua Bian, Jianyou Mao, Shuoning Li, Shangzhong Liu, Mingan Wang, Jiangchun Zhong *, Hongchao Guo *

Department of Applied Chemistry, China Agricultural University, 2 West Yuanmingyuan Road, Beijing 100193, PR China

ARTICLE INFO

Article history:
Received 14 May 2011
Accepted 14 June 2011
Available online 4 August 2011

ABSTRACT

The enantioselective Henry reaction between nitromethane and various aldehydes catalyzed by chiral amino alcohol–Zn complex was described. The resulting β-nitroalcohols were obtained in high yields and with moderate to good enantiomeric excesses.

© 2011 Elsevier Ltd. All rights reserved.

1. Introduction

The asymmetric Henry or nitroaldol reaction is one of the most useful carbon–carbon bond-forming reactions for the preparation of optically active β-nitroalcohols, which can be used as valuable starting materials for chiral 1,2-amino alcohols and β-hydroxyl carboxylic acids.[1,2] It is thus of great importance to explore new chiral catalysts for this reaction. Since the first enantioselective Henry reaction reported by Shibasaki in 1992,[3] various catalytic systems including chiral metal catalysts and organocatalysts have been developed.[2,4–8] Among all of the chiral catalysts reported so far, the classical Zn catalytic system has attracted much attention in terms of its operational simplicity and mild reaction conditions. In 2002, Trost reported the first dinuclear zinc-amino alcohol catalyzed asymmetric Henry reaction, providing the nitroaldol products in up to 93% ee and 90% yield.[9] Since then, several zinc catalytic systems have been developed for the asymmetric Henry reaction.[10–17] In these systems, amino alcohols were often used as chiral ligands. Palomo's *N*-methylephedrine–Zn could very efficiently catalyze the asymmetric Henry reaction to give nitroaldol products in excellent enantioselectivity (mostly above 90% ee).[12] Lin's bicyclo[3.3.0]octane-based β-amino alcohol–Zn,[13] Bulut and Dogan's ferrocenyl-substituted aziridinylmethanol–Zn[14] and Oh's brucine-derived amino alcohol–Zn[15] showed moderate catalytic capability and afforded poor to good enantioselectivity (generally below 90% ee). Reiser's *t*-Bu-leucin–Zn[16] and Demirel's imino alcohol–Zn[17] did not work efficiently and could only afford low yield and ee. In order to explore novel efficient amino alcohol–Zn systems, we conceived the possibility of introducing a new type of 1,4-amino alcohols based on the chiral cyclopropane backbone **1**–**5**, which might serve as an excellent chiral ligand in the asymmetric Henry reaction (Scheme 1).

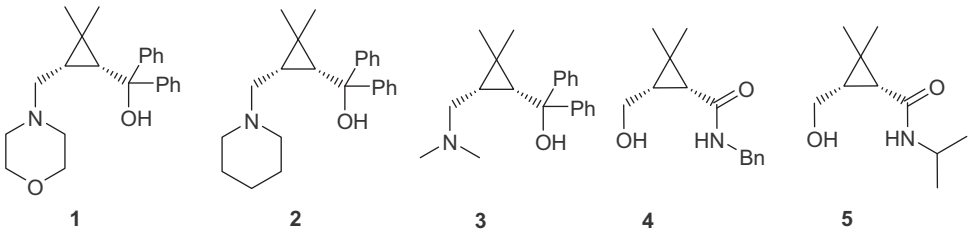
In our previous studies, a series of chiral amino alcohols based on the cyclopropane backbone have been developed and applied in the addition of dialkylzinc or alkyne derivatives to aldehydes, affording excellent enantioselectivity.[18] As part of a continuing effort to develop enantioselective reactions, we have examined these 1,4-amino alcohols in the asymmetric Henry reactions. Herein, we report the enantioselective Henry reaction between nitromethane and a wide range of aldehydes catalyzed by the zinc complexes of the chiral 1,4-amino alcohol.

2. Results and discussion

Initially, in the presence of 10 mol % of ligand **1**, the Henry reaction of benzaldehyde and nitromethane was carried out for the reaction conditions screen. The amino alcohol **1** was firstly mixed with the Me_2Zn in dichloromethane at 0 °C and then incubated for 30 min to form chiral zinc-catalyst, after which the reaction temperature was decreased to −50 °C. After the aldehyde and nitromethane were added, the reaction temperature was increased to −30 °C, and the reaction mixture was stirred for 48 h to give 2-nitro-1-phenylethanol in 70% yield and 77% ee (Table 1, entry 1). When toluene and chloroform were used as the solvent under otherwise identical conditions, the reaction produced the corresponding product in 79% ee and 78% ee, albeit in lower 56% yield and 51% yield, respectively (entries 2 and 3). When the amount of nitromethane was increased from 8 to 10 equiv; the reaction yield and ee were slightly improved to 78% and 82%, respectively (Table 1, entry 4). The amount was continuously increased to 20 equiv, the yield and ee of the corresponding product dropped to 70% and 76%, respectively (entry 5). The temperature effect was also tested using 10 equiv of nitromethane. The reaction temperature was raised from −30 to −20 °C, and the results remained nearly unchanged (Table 1, entry 6). However, increasing the temperature further to 0 °C resulted in the deteriorated 75% ee. Although reducing the catalyst loading to 5 mol % had only a slightly negligible influence on enantioselectivity, a sharp drop in

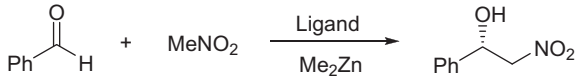
* Corresponding authors. Tel.: +86 010 62731356; fax: +86 010 62820325.
E-mail addresses: dr_zhongjiangchun@yahoo.com.cn (J. Zhong), hchguo@gmail.com (H. Guo).

0957-4166/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2011.06.032



Scheme 1. Cyclopropane amino alcohol **1**.

Table 1
Optimization of reaction conditions for the enantioselective Henry reaction



Entry	CH_3NO_2 (equiv)	Ligand (mol %)	T (°C)	Time (h)	Solvent	Yield[a] (%)	ee[b] (%)
1	8	**1**/10	−30	48	CH_2Cl_2	70	77
2	8	**1**/10	−30	48	Toluene	56	79
3	8	**1**/10	−30	48	CH_3Cl	51	78
4	10	**1**/10	−30	48	CH_2Cl_2	78	82
5	20	**1**/10	−30	48	CH_2Cl_2	70	76
6	10	**1**/10	−20	48	CH_2Cl_2	80	81
7	10	**1**/10	0	48	CH_2Cl_2	82	75
8	10	**1**/5	−20	48	CH_2Cl_2	48	80
9	10	**1**/20	−20	48	CH_2Cl_2	95	80
10	10	**2**/10	−20	48	CH_2Cl_2	70	77
11	10	**3**/10	−20	48	CH_2Cl_2	67	69
12	10	**4**/10	−20	48	CH_2Cl_2	34	10
13	10	**5**/10	−20	48	CH_2Cl_2	46	13

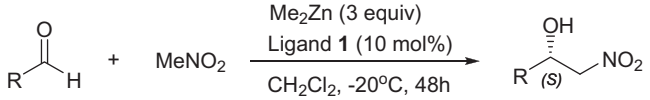
[a] Isolated yield.
[b] Determined by chiral HPLC analysis using a chiral stationary column. The absolute configuration was assigned as (*S*) by comparing their specific rotations with the literature data.

yield was observed (Table 1, entry 8). When the catalyst loading was increased to 20 mol %, the yield was enhanced to 95%, but the ee value remained at 80% (Table 1, entry 9). Under the optimized reaction conditions, other amino alcohols **2**–**5** were also examined, but they generally gave moderate results in the terms of both yield and ee (entries 10–13). Thus, the present reaction was best performed using 10 equiv of nitromethane with 10 mol % of ligand **1** in dichloromethane at −20 °C for 48 h.

Having established the optimized reaction conditions, various aldehydes were examined in order to explore the reaction scope; the results are shown in Table 2. The asymmetric Henry reaction of a variety of aldehydes with nitromethane took place, affording the anticipated 2-nitroalcohol products in good to excellent yields (65–90% yield) and with moderate to good enantioselectivity (55–84% ee). Phenyl aldehydes with electron-withdrawing or -donating substituents at the *ortho*-, *meta*-, and *para*-positions of the benzene rings worked well (entries 1–11), as did two naphthyl aldehydes (entries 12 and 13). The best 84% ee was obtained when 4-methylbenzaldehyde was used as a substrate. It is worth mentioning that furan-2-carbaldehyde and cinnamaldehyde also worked well, readily affording the corresponding 2-nitroalcohol in good yield and enantioselectivity (entries 14 and 15). The aliphatic aldehydes could also undergo the Henry reaction, providing the corresponding nitroaldol products in good yield, albeit in diminished enantioselectivity (entries 16–18).

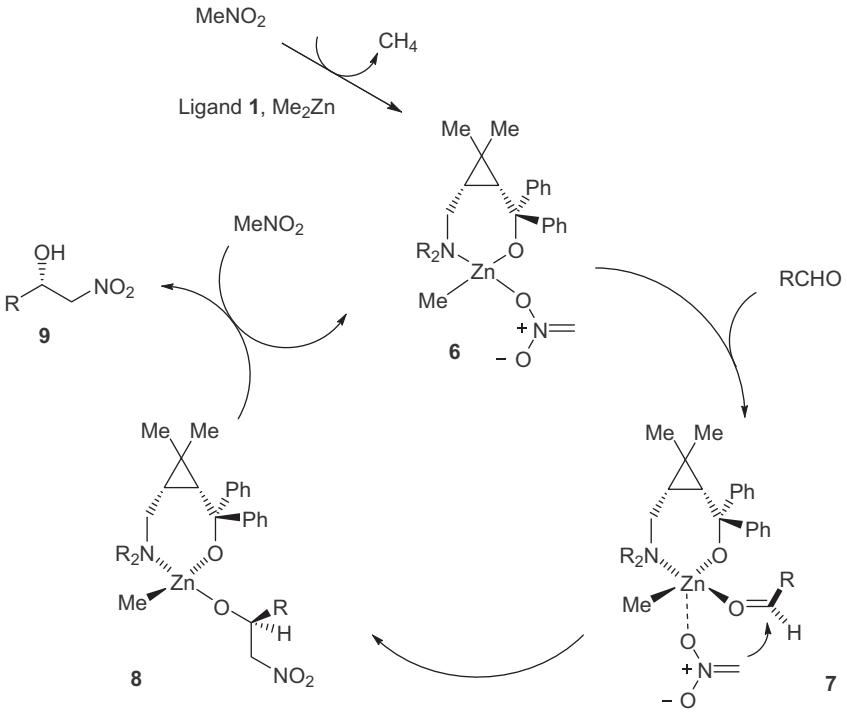
On the basis of the reported mechanistic studies on the asymmetric Henry reaction catalyzed by a Zn–amino alcohol system,[7a,9a] a plausible reaction mechanism is proposed (Scheme 2). It has been widely accepted that the catalysis cycle is typically initiated through the deprotonation of nitromethane by dimethylzinc in the presence of amino alcohol **1**, leading to the formation of a zinc complex intermediate **7**. The zinc-mediated dual activation of the nitronate and the aldehyde substrate assists the enantioselective carbon–carbon bond formation, resulting in the nitroaldol product.

Table 2
Enantioselective Henry reaction catalyzed by the Zn–amino alcohol system



Entry	Aldehyde	Yield[a] (%)	ee[b] (%)
1	Benzaldehyde	80	81
2	*p*-MeC_6H_4CHO	75	84
3	*o*-MeC_6H_4CHO	72	80
4	*o*-$MeOC_6H_4CHO$	82	83
5	*m*-$MeOC_6H_4CHO$	81	77
6	*p*-$MeOC_6H_4CHO$	75	82
7	*p*-BrC_6H_4CHO	80	78
8	*o*-ClC_6H_4CHO	90	80
9	*m*-ClC_6H_4CHO	75	72
10	*o*-FC_6H_4CHO	68	80
11	*p*-FC_6H_4CHO	72	78
12	1-Naphthaldehyde	80	74
13	2-Naphthaldehyde	78	78
14	Furan-2-carbaldehyde	65	70
15	Cinnamaldehyde	70	78
16	Cyclohexanecarbaldehyde	77	60
17	*n*-Heptanal	82	62
18	*iso*-Butyraldehyde	80	55

[a] Isolated yield.
[b] Determined by chiral HPLC analysis using a chiral stationary column. The absolute configuration was assigned as (*S*) by comparing their specific rotations with the literature data.



Scheme 2. Proposed catalytic cycle.

3. Conclusion

In conclusion, we have developed a novel amino alcohol–zinc catalyst catalyzed asymmetric Henry reaction which affords the corresponding β-nitroalcohols in moderate to good enantioselectivity and high yield. This catalytic system can be applied to a wide range of aldehydes including aromatic, α,β-unsaturated and aliphatic aldehydes. The applications of this zinc-amino alcohol system in other asymmetric reactions are currently being carried out in this laboratory and will be reported in due course.

4. Experimental

4.1. General

All reactions were performed under a nitrogen atmosphere in oven-dried glassware with magnetic stirring. Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Dichloromethane was distilled from $LiAlH_4$ under nitrogen. Organic solutions were concentrated under reduced pressure using a rotary evaporator or oil pump. Reactions were monitored through thin-layer chromatography (TLC) on silica gel-precoated glass plates. Chromatograms were visualized by fluorescence quenching under UV light at 254 nm. Flash column chromatography was performed using Qingdao Haiyang flash silica gel (200–300 mesh). ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using a Bruker DRX 500 spectrometer (referenced internally to Me_4Si); coupling constants (J) are measured in Hertz. Mass spectra were recorded on an Agilent instrument using the TOF MS technique. Accurate mass measurements were performed using an Agilent instrument with the ESI-MS technique and samples were dissolved in $CHCl_3$. The optical rotations were measured with a Perkin–Elmer PE-341 polarimeter. High performance liquid chromatography was conducted on an Agilent 1100 using a chiral column Diacel Chiralcel OD-H or AD-H. Retention time is given in minutes.

4.2. General procedure for the asymmetric nitroaldol reaction

A solution of Me_2Zn (2.5 mL, 1.2 M in toluene, 3 mmol, 3 equiv) was added to a solution of amino alcohol ligand (35 mg, 0.1 mmol, 0.1 equiv) in 2 mL of dichloromethane at 0 °C under an atmosphere of nitrogen. After 30 min, the mixture was cooled to −50 °C and $MeNO_2$ (0.54 mL, 10 mmol) was added in one portion followed by the aldehyde (1 mmol). The resulting reaction mixture was stirred for 1 h, then the reaction temperature was increased to −20 °C and stirred for 48 h. The reaction was quenched by the addition of the saturated NH_4Cl (10 mL) and the mixture was extracted with ether (10 mL × 3). The organic layers were combined and dried over anhydrous Na_2SO_4, and then concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexanes = 1:9) to give the corresponding product as a colorless oil.

4.2.1. (*S*)-2-Nitro-1-phenylethanol

Yield 80%, 81% ee determined by HPLC with a Chiralpak OD column (20% isopropanol in hexane, 1 mL/min, 230 nm) analysis. Rention time: t_{major} = 9.7 min, t_{minor} = 8.2 min. $[\alpha]_D^{20} = +29.7$ (c 2.4, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.42–7.35 (m, 5H), 5.43 (dd, J = 3.0 Hz, 9.5 Hz, 1H), 4.59 (dd, J = 9.5 Hz, 13.5 Hz, 1H), 4.49 (dd, J = 3.0 Hz, 13.5 Hz, 1H), 3.08 (s, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 129.0, 128.9, 126.0, 81.2, 71.0 ppm. HRMS (TOF) calcd for $C_8H_9NNaO_3^+$ $[M+Na]^+$: 190.0475; found: 190.0477.

4.2.2. (*S*)-2-Nitro-1-(*p*-tolyl)ethanol

Yield 75%, 84% ee determined by HPLC with a Chiralpak OD column (20% isopropanol in hexane, 1 mL/min, 230 nm) analysis. Rention time: t_{major} = 10.0 min, t_{minor} = 8.3 min. $[\alpha]_D^{20} = +34.1$ (c 1.9, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, J = 8.0 Hz, 2H),

7.21 (d, J = 8.0 Hz, 2H), 5.42 (dd, J = 2.5 Hz, 9.5 Hz, 1H), 4.59 (dd, J = 10.0 Hz, 13.0 Hz, 1H), 4.48 (dd, J = 3.0 Hz, 13.5 Hz, 1H), 2.80 (s, 1H), 2.39 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0, 135.2, 129.7, 125.9, 81.3, 71.0, 21.2 ppm. HRMS (TOF) calcd for $C_9H_{11}NNaO_3^+$ $[M+Na]^+$: 204.0631; found: 204.0625.

4.2.3. (*S*)-2-Nitro-1-(*o*-tolyl)ethanol

Yield 72%, 80% ee determined by HPLC with a Chiralpak OD column (20% isopropanol in hexane, 1 mL/min, 230 nm) analysis. Rention time: t_{major} = 10.2 min, t_{minor} = 7.0 min. $[\alpha]_D^{20} = +31.1$ (c 2.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.49 (m, 2H), 7.27–7.23 (m, 2H), 7.19–7.17 (m, 1H), 5.66 (dd, J = 2.5 Hz, 9.5 Hz, 1H), 4.53 (dd, J = 9.5 Hz, 13.5 Hz, 1H), 4.42 (dd, J = 2.5 Hz, 13.5 Hz, 1H), 2.74 (s, 1H), 2.38 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.2, 134.5, 130.9, 128.7, 126.8, 125.6, 80.2, 68.0, 18.9 ppm. HRMS (TOF) calcd for $C_{10}H_{13}NO_5^+$ $[M+HCOOH]^+$: 227.0794; found: 227.0760.

4.2.4. (*S*)-2-Nitro-1-(4-methoxyphenyl)ethanol

Yield 82%, 83% ee determined by HPLC with a Chiralpak OD column (20% isopropanol in hexane, 1 mL/min, 230 nm) analysis. Rention time: t_{major} = 13.0 min, t_{minor} = 10.7 min. $[\alpha]_D^{20} = +19.0$ (c 2.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (dd, J = 2.0 Hz, 6.5 Hz, 2H), 6.90 (dd, J = 2.0 Hz, 6.5 Hz, 2H), 5.53–5.42 (m, 1H), 4.75–4.61 (m, 1H), 4.54–4.29 (m, 1H), 3.80 (s, 1H), 2.94 (s, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0, 130.3, 127.3, 114.4, 81.3, 70.7, 55.4 ppm. HRMS (TOF) calcd for $C_9H_{11}NNaO_4^+$ $[M+Na]^+$: 220.0580; found: 220.0587.

4.2.5. (*S*)-1-(3-Methoxyphenyl)-2-nitroethanol

Yield 81%, 77% ee determined by HPLC with a Chiralpak OD column (20% isopropanol in hexane, 1 mL/min, 230 nm) analysis. Rention time: t_{major} = 16.2 min, t_{minor} = 12.6 min. $[\alpha]_D^{20} = +24.8$ (c 2.6, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.26 (m, 1H), 6.95–6.94 (m, 2H), 6.89–6.87 (m, 1H), 5.42–5.39 (m, 1H), 4.58 (dd, J = 9.5 Hz, 13.5 Hz, 1H), 4.49 (dd, J = 3.0 Hz, 13.5 Hz, 1H), 3.81 (s, 1H), 3.04 (d, J = 4.0 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1, 139.8, 130.1, 118.1, 114.4, 111.5, 81.2, 70.9, 55.3 ppm. HRMS (TOF) calcd for $C_9H_{11}NNaO_4^+$ $[M+Na]^+$: 220.0580; found: 220.0577.

4.2.6. (*S*)-1-(2-Methoxyphenyl)-2-nitroethanol

Yield 75%, 82% ee determined by HPLC with a Chiralpak OD column (20% isopropanol in hexane, 1 mL/min, 230 nm) analysis. Rention time: t_{major} = 8.5 min, t_{minor} = 7.5 min. $[\alpha]_D^{20} = +36.6$ (c 1.8, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (dd, J = 1.5 Hz, 7.5 Hz, 1H), 7.34–7.30 (m, 1H), 7.01–6.98 (m, 1H), 6.90 (d, J = 8.0 Hz, 1H), 5.62–5.59 (m, 1H), 4.63 (dd, J = 3.5 Hz, 13.0 Hz, 1H), 4.55 (dd, J = 9.0 Hz, 13.0 Hz, 1H), 3.87 (s, 1H), 3.25 (d, J = 6.0 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 129.8, 127.2, 126.1, 121.2, 110.6, 79.9, 67.8, 55.4 ppm. HRMS (TOF) calcd for $C_9H_{11}NNaO_4^+$ $[M+Na]^+$: 220.0580; found: 220.0583.

4.2.7. (*S*)-1-(1-Naphthyl)-2-nitroethanol

Yield 80%, 74% ee determined by HPLC with a Chiralpak OD column (20% isopropanol in hexane, 1 mL/min, 230 nm) analysis. Rention time: t_{major} = 15.2 min, t_{minor} = 10.0 min. $[\alpha]_D^{20} = +12.5$ (c 1.9, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 8.5 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.86 (d, J=8.5 Hz, 1H), 7.76 (d, J = 7.5 Hz, 1H), 7.61–7.58 (m, 1H), 7.56–7.50 (m, 2H), 6.27–6.24 (m, 1H), 4.70–4.63 (m, 2H), 2.93 (d, J = 3.5 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.8, 133.6, 129.6, 129.5, 129.4, 127.1, 126.2, 125.6, 123.9, 121.9, 80.8, 68.4 ppm. HRMS (TOF) calcd for $C_{12}H_{11}NNaO_3^+$ $[M+Na]^+$: 240.0631; found: 240.0637.

4.2.8. (*S*)-2-Nitro-1-(2-naphthyl)ethanol

Yield 78%, 78% ee determined by HPLC with a Chiralpak OD column (20% isopropanol in hexane, 1 mL/min, 230 nm) analysis. Rention time: t_{major} = 29.9 min, t_{minor} = 21.2 min. $[\alpha]_D^{20} = +28.4$ (c 2.8, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88–7.84 (m, 4H), 7.54–7.51 (m, 2H), 7.46 (d, J = 9.0 Hz, 1H), 5.62 (d, J = 9.5 Hz, 1H), 4.68 (dd, J = 10.0 Hz, 13.5 Hz, 1H), 4.59 (dd, J = 3.0 Hz, 13.5 Hz, 1H), 2.93 (d, J = 3.0 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.4, 133.5, 133.2, 129.1, 128.1, 127.8, 126.8, 126.7, 125.4, 123.2, 81.2, 71.2 ppm. HRMS (TOF) calcd for $C_{12}H_{11}NNaO_3^+$ $[M+Na]^+$: 240.0631; found: 240.0629.

4.2.9. (*S*)-1-(4-Fluorophenyl)-2-nitroethanol

Yield 72%, 78% ee determined by HPLC with a Chiralpak OD column (20% isopropanol in hexane, 1 mL/min, 230 nm) analysis. Rention time: t_{major} = 7.8 min, t_{minor} = 6.8 min. $[\alpha]_D^{20} = +28.7$ (c 2.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.38 (m, 2H), 7.11–7.08 (m, 2H), 5.47–5.44 (m, 1H), 4.58 (dd, J = 9.5 Hz, 13.5 Hz, 1H), 4.49 (dd, J = 3.0 Hz, 13.5 Hz, 1H), 2.87 (d, J = 3.5 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 133.9, 127.8, 115.9, 81.1, 70.4 ppm. HRMS (TOF) calcd for $C_9H_{10}FNO_5^+$ $[M+HCOOH]^+$: 231.0543; found: 231.0476.

4.2.10. (*S*)-1-(2-Fluorophenyl)-2-nitroethanol

Yield 68%, 80% ee determined by HPLC with a Chiralpak OD column (20% isopropanol in hexane, 1 mL/min, 230 nm) analysis. Rention time: t_{major} = 15.5 min, t_{minor} = 14.8 min. $[\alpha]_D^{20} = +30.9$ (c 1.8, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57–7.55 (m, 1H), 7.38–7.33 (m, 1H), 7.24–7.20 (m, 1H), 7.10–7.07 (m, 1H), 5.75 (dd, J = 3.5 Hz, 9.0 Hz, 1H), 4.63 (dd, J = 3.5 Hz, 14.0 Hz, 1H), 4.59 (dd, J = 9.0 Hz, 13.5 Hz, 1H), 2.95 (s, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 130.5, 127.6, 125.1, 115.7, 115.5, 79.7, 65.5 ppm. HRMS (TOF) calcd for $C_9H_{10}FNO_5^+$ $[M+HCOOH]^+$: 231.0543; found: 231.0515.

4.2.11. (*S*)-1-(3-Chlorophenyl)-2-nitroethanol

Yield 75%, 72% ee determined by HPLC with a Chiralpak OD column (2% isopropanol in hexane, 1 mL/min, 230 nm) analysis. Rention time: t_{major} = 9.3 min, t_{minor} = 7.8 min. $[\alpha]_D^{20} = +30.7$ (c 2.6, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.34–7.33 (m, 2H), 7.29–7.26 (m, 1H), 5.45 (dd, J = 2.5 Hz, 9.5 Hz, 1H), 4.58 (dd, J = 9.5 Hz, 13.5 Hz, 1H), 4.51 (dd, J = 3.0 Hz, 13.5 Hz, 1H), 2.97 (s, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.0, 135.1, 130.3, 129.1, 126.2, 124.1, 80.9, 70.3 ppm. HRMS (TOF) calcd for $C_9H_{10}ClNO_5^+$ $[M+HCOOH]^+$: 247.0248; found: 247.0200.

4.2.12. (*S*)-1-(2-Chlorophenyl)-2-nitroethanol

Yield 90%, 80% ee determined by HPLC with a Chiralpak OD column (2% isopropanol in hexane, 1 mL/min, 230 nm) analysis. Rention time: t_{major} = 8.7 min, t_{minor} = 8.3 min. $[\alpha]_D^{20} = +40.4$ (c 2.7, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66–7.65 (m, 1H), 7.39–7.34 (m, 2H), 7.32–7.29 (m, 1H), 5.85–5.82 (m, 1H), 4.67 (dd, J = 2.5 Hz, 13.5 Hz, 1H), 4.45 (dd, J = 9.5 Hz, 14.0 Hz, 1H), 3.11 (d, J = 4.0 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.6, 131.6, 130.0, 129.8, 127.6, 127.5, 79.4, 67.9 ppm. HRMS (TOF) calcd for $C_8H_8ClNNaO_3^+$ $[M+Na]^+$: 224.0085; found: 224.0093.

4.2.13. (*S*)-2-Nitro-1-(4-bromophenyl)ethanol

Yield 78%, 80% ee determined by HPLC with a Chiralpak OD column (20% isopropanol in hexane, 1 mL/min, 230 nm) analysis. Rention time: t_{major} = 10.7 min, t_{minor} = 8.5 min. $[\alpha]_D^{20} = +27.5$ (c 2.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54–7.52 (m, 2H), 7.29–7.26 (m, 2H), 5.44–5.41 (m, 1H), 4.57 (dd, J = 9.5 Hz, 13.5 Hz, 1H), 4.49 (dd, J = 3.0 Hz, 13.5 Hz, 1H), 2.99 (d, J = 3.5 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1, 132.2, 127.6, 123.0, 80.9, 70.4 ppm.

HRMS (TOF) calcd for $C_8H_8BrNNaO_3^+$ [M+Na]$^+$: 267.9580; found: 267.9587.

4.2.14. (*S*)-1-(Furan-2-yl)-2-nitroethanol

Yield 65%, 70% ee determined by HPLC with a Chiralpak AD column (5% isopropanol in hexane, 1 mL/min, 210 nm) analysis. Rention time: t_{major} = 20.7 min, t_{minor} = 19.2 min. $[\alpha]_D^{20} = +22.5$ (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CHCl_3$) δ: 7.42–7.41 (m, 1H), 6.41–6.37 (m, 2H), 5.50–5.44 (m, 1H), 4.78 (dd, *J* = 9.0 Hz, 13.5 Hz, 1H), 4.67 (dd, *J* = 3.6 Hz, 13.5 Hz, 1H), 3.10 (d, *J* = 5.3 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CHCl_3$) δ: 150.8, 143.1, 110.6, 108.1, 78.4, 64.8 ppm. HRMS (TOF) calcd for $C_6H_7NNaO_4^+$ [M+Na]$^+$: 180.0268, found: 180.0270.

4.2.15. (*S*)-1-Nitro-4-phenyl-but-3-en-2-ol

Yield 70%, 78% ee determined by HPLC with a Chiralpak OD column (20% isopropanol in hexane, 1 mL/min, 230 nm) analysis. Rention time: t_{major} = 19.2 min, t_{minor} = 21.9 min. $[\alpha]_D^{20} = +14.9$ (*c* 1.8, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.38 (m, 2H), 7.36–7.33 (m, 2H), 7.31–7.29 (m, 1H), 6.80 (d, *J* = 16.0 Hz, 1H), 6.15 (dd, *J* = 6.0 Hz, 16.0 Hz, 1H), 5.09–5.04 (m, 1H), 4.55–4.49 (m, 2H), 2.60 (d, *J* = 4.0 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.5, 133.8, 128.8, 128.6, 126.7, 124.9, 79.9, 69.6 ppm. HRMS (TOF) calcd for $C_{10}H_{11}NNaO_3^+$ [M+Na]$^+$: 216.0631; found: 216.0631.

4.2.16. (*S*)-1-Cyclohexyl-2-nitro-ethanol

Yield 77%, 60% ee determined by HPLC with a Chiralpak AD column (10% isopropanol in hexane, 1 mL/min, 220 nm) analysis. Rention time: t_{major} = 27.5 min, t_{minor} = 25.2 min. $[\alpha]_D^{20} = +13.0$ (*c* 3.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.50–4.40 (m, 2H), 4.11–4.09 (m, 1H), 2.46 (s, 1H), 1.85–1.77 (m, 3H), 1.71–1.66 (m, 2H), 1.49–1.46 (m, 1H), 1.28–1.08 (m, 5H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 79.4, 72.9, 41.5, 28.9, 28.0, 26.1, 25.9, 25.8 ppm. HRMS (TOF) calcd for $C_8H_{15}NNaO_3^+$ [M+Na]$^+$: 196.0944; found: 196.0942.

4.2.17. (*S*)-1-Nitrooctan-2-ol

Yield 82%, 62% ee determined by HPLC with a Chiralpak AD column (10% isopropanol in hexane, 1 mL/min, 220 nm) analysis. Rention time: t_{major} = 11.6 min, t_{minor} = 7.7 min. $[\alpha]_D^{20} = +6.2$ (*c* 1.6, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.45–4.29 (m, 3H), 1.59–1.44 (m, 3H), 1.41–1.24 (m, 7H), 0.89 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 80.7, 68.7, 33.8, 31.6, 29.0, 25.2, 22.5, 14.0 ppm. HRMS (TOF) calcd for $C_8H_{17}NNaO_3^+$ [M+Na]$^+$: 198.1101; found: 198.1094.

4.2.18. (*S*)-3-Methyl-1-nitro-2-butanol

Yield 80%, 55% ee determined by HPLC with a Chiralpak OD column (2% isopropanol in hexane, 1 mL/min, 220 nm) analysis. Rention time: t_{major} = 20.6 min, t_{minor} = 18.7 min. $[\alpha]_D^{20} = +11.3$ (*c* 2.3, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.48 (dd, *J* = 2.5 Hz, 13.5 Hz, 1H), 4.41 (dd, *J* = 9.5 Hz, 13.5 Hz, 1H), 4.12–4.10 (m, 1H), 2.48 (d, *J* = 4.5 Hz, 1H), 1.83–1.78 (m, 1H), 1.00 (t, *J* = 7.0 Hz, 6H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 79.3, 73.4, 31.8, 18.5, 17.5 ppm. HRMS (TOF) calcd for $C_5H_{12}NO_3^+$ [M+H]$^+$: 134.0812; found: 134.0816.

Acknowledgments

This work was financially supported by the startup research funding of China Agricultural University, Chinese Universities Scientific Fund (Project Nos. 2009JS45, 2010JS028, 2011JS029 and 2011JS031), National 12th Five-Year Plan Scientific and Technological Issues, NSFC and Nutriechem Company.

References

1. (a) Rosini, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 2, pp 321–340; (b) Shibasaki, M.; Gröer, H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; vol. III, pp 1075–1090; (c) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001.
2. For reviews on the catalytic asymmetric Henry reaction, see: (a) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915–945; (b) Palomo, C.; Oiarbide, M.; Mielgo, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5442–5444; (c) Boruwa, J.; Gogoi, N.; Saikia, P. P.; Barua, N. C. *Tetrahedron: Asymmetry* **2006**, *17*, 3315–3326; (d) Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, 2561–2574; (e) Marqués-López, E.; Merino, P.; Tejero, T.; Herrera, R. P. *Eur. J. Org. Chem.* **2009**, 2401–2420.
3. Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418–4420.
4. For a selected example of a Co-catalyzed asymmetric Henry reaction, see: Park, J.; Lang, K.; Abboud, K. A.; Hong, S. *J. Am. Chem. Soc.* **2008**, *130*, 16484–16485.
5. Selected examples of the Cr-catalyzed asymmetric Henry reaction: (a) Kowalczyk, R.; Kwiatkowski, P.; Skarżewski, J.; Jurczak, J. *J. Org. Chem.* **2009**, *74*, 753–756; (b) Zulauf, A.; Mellah, M.; Schulz, E. *J. Org. Chem.* **2009**, *74*, 2242–2245.
6. Selected example of a Mg-catalyzed asymmetric Henry reaction: Choudary, B. M.; Ranganath, K. V. S.; Kantam, U.; Pal, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, *127*, 13167–13171.
7. Selected examples for Cu-catalyzed asymmetric Henry reaction: (a) Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692–12693; (b) Arai, T.; Watanabe, M.; Fujiwara, A.; Yokoyama, N.; Yanagisawa, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5978–5981; (c) Gan, C.; Lai, G.; Zhang, Z.; Wang, Z.; Zhou, M. *Tetrahedron: Asymmetry* **2006**, *17*, 725–728; (d) Lai, G.; Wang, S.; Wang, Z. *Tetrahedron: Asymmetry* **2008**, *19*, 1813–1819; (e) Blay, G.; Climent, E.; Fernández, I.; Hernández-Olmos, V.; Pedro, J. R. *Tetrahedron: Asymmetry* **2007**, *18*, 1603–1612; (f) Jiang, J.; Shi, M. *Tetrahedron: Asymmetry* **2007**, *18*, 1376–1382; (g) Ma, K.; You, J. *Chem. Eur. J.* **2007**, *13*, 1863–1871; (h) Qin, B.; Xiao, X.; Liu, X.; Huang, J.; Wen, Y.; Feng, X. *J. Org. Chem.* **2007**, *72*, 9323–9328; (i) Arai, T.; Yokoyama, N.; Yanagisawa, A. *Chem. Eur. J.* **2008**, *15*, 2052–2059; (j) Rachwalski, M.; Leśniak, S.; Sznajder, E.; Kiezbasiński, P. *Tetrahedron: Asymmetry* **2009**, *20*, 1547–1549; (k) Mayani, V. J.; Abdi, S. H. R.; Kureshy, R. I.; Khan, N. H.; Das, A.; Bajaj, H. C. *J. Org. Chem.* **2010**, *75*, 6191–6195.
8. For selected examples of organocatalyst-catalyzed asymmetric Henry reaction, see: (a) Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 929–931; (b) Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392–12393.
9. (a) Trost, B. M.; Yeh, V. S. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 861–863; (b) Trost, B. M.; Yeh, V. S. C.; Ito, H.; Bremeyer, N. *Org. Lett.* **2002**, *4*, 2621–2623.
10. Liu, S.; Wolf, C. *Org. Lett.* **2008**, *10*, 1831–1834.
11. (a) Gao, J.; Martell, A. E. *Org. Biomol. Chem.* **2003**, *1*, 2801–2806; (b) Gao, J.; Zingaro, R. A.; Reibenspies, J. H.; Martell, A. E. *Org. Lett.* **2004**, *6*, 2453–2455.
12. Palomo, C.; Oiarbide, M.; Laso, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3881–3884.
13. Zhong, Y. W.; Tian, P.; Lin, G. Q. *Tetrahedron: Asymmetry* **2004**, *15*, 771–776.
14. Bulut, A.; Aslan, A.; Dogan, Ö. *J. Org. Chem.* **2008**, *73*, 7373–7375.
15. Kim, H. Y.; Oh, K. *Org. Lett.* **2009**, *11*, 5682–5685.
16. Klein, G.; Pandiaraju, S.; Reiser, O. *Tetrahedron Lett.* **2002**, *43*, 7503–7506.
17. Çolak, M.; Aral, T.; Hoşgören, H.; Demirel, N. *Tetrahedron: Asymmetry* **2007**, *18*, 1129–1133.
18. (a) Zhong, J.; Guo, H.; Wang, M.; Yin, M.; Wang, M. *Tetrahedron: Asymmetry* **2007**, *18*, 734–741; (b) Zhong, J.; Wang, M.; Guo, H.; Yin, M.; Bian, Q.; Wang, M. *Synlett* **2006**, 1667–1670; (c) Zhong, J.; Hou, S.; Bian, Q.; Yin, M.; Na, R.; Zheng, B.; Li, Z.; Liu, S.; Wang, M. *Chem. Eur. J.* **2009**, *15*, 3069–3071; (d) Zheng, B.; Hou, S.; Li, Z.; Guo, H.; Zhong, J.; Wang, M. *Tetrahedron: Asymmetry* **2009**, *20*, 2125–2129; (e) Li, Z.; Wang, M.; Bian, Q.; Zheng, B.; Mao, J.; Li, S.; Liu, S.; Wang, M.; Zhong, J.; Guo, H. *Chem. Eur. J.* **2011**, *17*, 5782–5786.