Tetrahedron: *Asymmetry* 23 (2012) 124–129

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

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

A highly chemo- and enantioselective nitroaldol reaction of haloenals: preparation of chiral functionalized allylic alcohols

Lianghu Gu, Yirong Zhou, Jingli Zhang, Yuefa Gong *

School of Chemistry and Chemical Engineering, Huazhong University of Science and Technology, 1037 Luoyu Road, Wuhan 430074, People's Republic of China

ARTICLE INFO

Article history:
Received 6 December 2011
Accepted 5 January 2012
Available online 18 February 2012

ABSTRACT

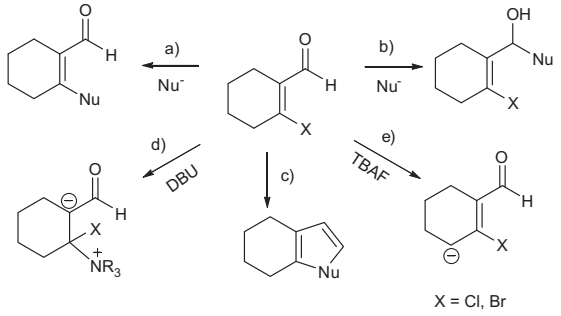
An efficient **L1**/Cu(II)-catalyzed highly chemoselective and enantioselective nitroaldol reaction of α- or β-haloenals with nitromethane has been described. The reaction delivered chiral functionalized allylic alcohols bearing halo and nitro groups with excellent results (up to 94% yield and 99% ee) under mild reaction conditions.

1. Introduction

Henry (nitroaldol) reactions between nitroalkanes and aldehydes provide valuable intermediates β-hydroxy nitroalkanes, which can be transformed into β-amino alcohols, aziridines, α-hydroxy carboxylic acids, and other complex target compounds.[1] In recent years, much progress has been made in the enantioselective version of the Henry reaction by developing various new chiral ligands. In this work, much attention has mainly been focused on the reaction of simple aromatic and aliphatic aldehydes.[2,3]

As useful building blocks, haloenals are usually employed for constructing versatile heterocyclic compounds,[4] carbocycles,[5] and quaternary carbon centers.[6] The halo atom on the C=C bond in the enal is activated by the electron-withdrawing carbonyl group, and can be readily replaced by other functional groups. As shown in Scheme 1, the presence of two reactive sites (C=O and =C–X) in the haloenal molecule makes it possible to follow different pathways under basic conditions, such as paths (a),[4b,c,7] (b)[5,8] and (c).[4d,e,9] Recently, Ma et al. reported a DBU-promoted Morita-Baylis–Hillman reaction[10] and Michael addition reaction[6a] of haloenals (path d). We have developed a novel TBAF-promoted intermolecular crossed reaction between haloenals and electron-deficient olefins, in which the vinylogous enolates generated by the deprotonation at the γ-position preferred to combine with the Michael acceptors at their α-position (path e).[6b]

Very recently, we developed an efficient chiral secondary diamine ligand for the copper-catalyzed asymmetric nitroaldol reaction.[3d] As a continuation of this work, we wondered what would happen between a haloenal and a nitroalkane in the presence of a catalyst, especially with regard to the chemoselectivity and enantioselectivity during the reaction. To the best of our knowledge, the asymmetric nitroaldol reaction of haloenals with nitromethane has not been reported. Thus, we attempted the reaction between haloenals and nitromethane in the presence of the Cu(II)-diamine system. This reaction proceeded smoothly and gave the nitroaldol products β-nitro allylic alcohols, which are important intermediates for a wide range of pharmaceutical substances and biologically active compounds because of their numerous synthetic applications.[11] Herein, we report the details of the highly chemo- and enantioselective reaction between haloenals and nitromethane.



Scheme 1. Possible reaction modes of β-haloenals under base conditions.

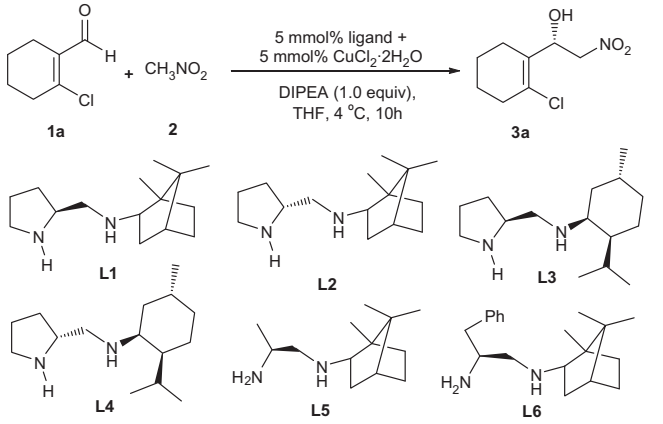
2. Results and discussion

Initially, we chose the reaction of 2-chlorocyclohex-1-enecarbaldehyde **1a** with nitromethane **2** as the model reaction (Table 1). Based on our previous work,[3d] several ligands and copper(II) chloride were utilized in the reaction with diisopropylethylamine (DIPEA) as the additive base in THF at 4 °C. Among the ligands **L1**–**L6**, **L1** was found to be a potentially useful one for the reaction and gave product **3a** in a 48% yield with 87% enantiomeric excess after 10 h (entry 1). When ligand **L2**, derived from D-proline, was

* Corresponding author. Tel./fax: +86 027 87543632.
E-mail address: gongyf@mail.hust.edu.cn (Y. Gong).

0957-4166/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2012.01.011

Table 1
Ligand screening[a]



Entry	Ligand	Yield[b]	ee[c] (%)
1	**L1**	48	87
2	**L2**	45	−31
3	**L3**	36	73
4	**L4**	43	−36
5	**L5**	43	74
6	**L6**	50	80

[a] Reactions were carried out on a 0.5 mmol scale of **1a** with 10 equiv of nitromethane in a mixture of 2.0 mL of THF, 5 mol % of ligand and 5 mol % of $CuCl_2{\cdot}2H_2O$ in the presence of 1.0 equiv of DIPEA at 4 °C for 10 h.
[b] Isolated yield, approx. 50% of **1a** was recovered.
[c] Ee was determined by HPLC analysis using Chiracel AD-H as a column.

used instead, the opposite (*R*)-configuration product was obtained with much lower enantioselectivity (entry 2). A similar change in stereoselectivity was also observed in the cases of **L3** and **L4** derived from (+)-(1*S*,2*S*,5*R*)-menthylamine, but their enantioselectivities were relatively poor. Ligands **L5** and **L6** also gave inferior results (entries 5 and 6).

Further optimization was carried out by assessing copper salts, bases, and solvents. Among the copper salts listed in Table 2, $CuCl_2{\cdot}2H_2O$, $Cu(OAc)_2{\cdot}H_2O$, and CuCl gave high ee values with little differences in the yields (entries 1, 2, and 6). For the best enantioselectivity, CuCl was chosen to estimate further the reaction solvents. In nitromethane, an improved yield but much lower ee value was observed in comparison to that in THF (entry 10). In view of the enantioselectivity, THF proved to be the most suitable solvent for this reaction (entries 1 and 9–13).

Next, various bases were tested by utilizing a CuCl/**L1** catalytic system in THF at 4 °C (entries 14–18). A satisfactory enantioselectivity was achieved when *N*-methylmorpholine (NMM) was used as the base additive, with an ee value of up to 94% being achieved (entry 18). Thus, NMM was finally chosen as the additive to further optimize the reaction conditions. Since nearly the same ee values were observed previously in the cases of $CuCl_2{\cdot}2H_2O$, $Cu(OAc)_2{\cdot}H_2O$, and CuCl (entries 1, 2, and 6), we examined the copper salts again by changing DIPEA into NMM (entries 19 and 20). As a consequence, $CuCl_2{\cdot}2H_2O$ gave the highest ee (96%), while $Cu(OAc)_2{\cdot}H_2O$ provided the highest yield up to 80% with 95% ee. In addition to the nitroaldol product, a certain amount of dehydrated side-product nitroolefin was obtained during the reaction. In order to avoid the dehydration, we tried to perform the reactions at a lower temperature (Table 3, entries 1–3). At −20 °C, **3a** was afforded in a 88% yield with 99% ee using $Cu(OAc)_2{\cdot}H_2O$ (entry 3). The effect of the amount of nitromethane was also evaluated (entries 4 and 5). The highest yield was achieved when 20 equiv of nitromethane were added, while the ee value remained the same. A further increase in the amount of nitromethane caused a decrease in both the ee value and the yield.

Table 2
Optimization of reaction parameters[a]

Entry	Copper salt	Solvent	Base	Yield[b] (%)	ee[c] (%)
1	$CuCl_2{\cdot}2H_2O$	THF	DIPEA	48	87
2	$Cu(OAc)_2{\cdot}H_2O$	THF	DIPEA	68	88
3	$CuBr_2$	THF	DIPEA	43	83
4	$CuSO_4{\cdot}5H_2O$	THF	DIPEA	20	27
5	CuCN	THF	DIPEA	52	79
6	CuCl	THF	DIPEA	60	90
7	CuBr	THF	DIPEA	50	78
8	CuI	THF	DIPEA	39	48
9	CuCl	CH_3OH	DIPEA	51	30
10	CuCl	$MeNO_2$	DIPEA	74	29
11	CuCl	MeCN	DIPEA	45	62
12	CuCl	CH_2Cl_2	DIPEA	35	20
13	CuCl	Et_2O	DIPEA	58	76
14	CuCl	THF	Et_3N	58	90
15	CuCl	THF	DMAP	10	28
16	CuCl	THF	Im[d]	22	42
17	CuCl	THF	pyridine	34	93
18	CuCl	THF	NMM	58	94
19	$CuCl_2{\cdot}2H_2O$	THF	NMM	48	96
20	$Cu(OAc)_2{\cdot}H_2O$	THF	NMM	80	95

[a] Reactions were carried out on a 0.5 mmol scale of **1a** with 10 equiv of nitromethane in a mixture of 2.0 mL of solvent, 5 mol % of ligand **L1** and 5 mol % of copper salts in the presence of 1.0 equiv of base at 4 °C for 12 h.
[b] Isolated yield (%).
[c] Determined by chiral HPLC analysis.
[d] Im = Imidazole.

Table 3
Reagent loading screening[a]

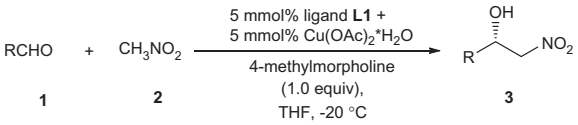
Entry	Copper salt	$MeNO_2$ (equiv)	Yield[b] (%)	ee[c] (%)
1	CuCl	10	58	97
2	$CuCl_2{\cdot}2H_2O$	10	62	98
3	$Cu(OAc)_2{\cdot}H_2O$	10	88	99
4	$Cu(OAc)_2{\cdot}H_2O$	20	94	99
5	$Cu(OAc)_2{\cdot}H_2O$	40	85	94

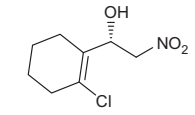
[a] Reactions were carried out on a 0.5 mmol scale of **1a** in a mixture of 2.0 mL of THF, 5 mol % of ligand **L1** and 5 mol % of copper salt in the presence of 1.0 equiv of NMM at −20 °C for 48 h.
[b] Isolated yield (%).
[c] Determined by chiral HPLC analysis.

On the basis of the optimized reaction parameters, the scope of haloenals was explored by treatment with 20 equiv of nitromethane in the presence of 5 mol % of **L1**/$Cu(OAc)_2{\cdot}H_2O$ and 1.0 equiv of NMM in THF at −20 °C (Table 4). With the cyclic haloenals **1a–f**, the reaction provided the expected products **3a–f** in high to excellent yields and with excellent enantioselectivities. In most cases, the ee values were above 95%, regardless of the size of the cyclic haloenals and the type of halo atoms at the β-position. With regards to the acyclic haloenals, the ee values varied remarkably with different substituent groups. Haloenals **1g** and **1h** gave much lower ee values. In addition, heteroaromatic haloenals **1k** was also tolerated, giving the desired product with good results. α-Haloenals **1i** and **1j** were also studied under the same conditions and different results were observed. It seems that the substituent group on the carbon near to the aldehyde group significantly influences the enantioselectivity of this reaction. Haloenals **1l–n** with bulky groups at the α-position provided the nitroaldol products **3l–n** with more than 95% ee values, albeit with a decrease in yield.

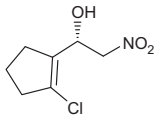
To account for the stereochemical outcome of this reaction, the absolute configuration of **4e** (solid) derived from **3e** (liquid) was confirmed by X-ray crystal analysis as shown in Figure 1. These

Table 4
Enantioselective Henry reaction of aldehydes with nitromethane[a,b,c,d]

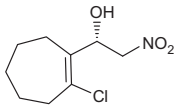




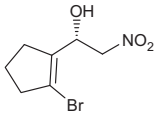
3a, 94% yield, 99% ee



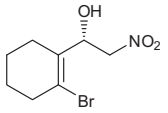
3b, 92% yield, 99% ee



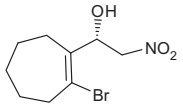
3c, 86% yield, 96% ee



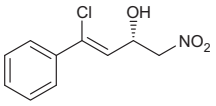
3d, 80% yield, 97% ee



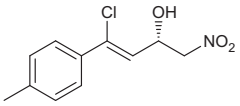
3e, 93% yield, 97% ee



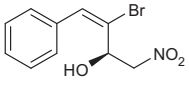
3f, 84% yield, 99% ee



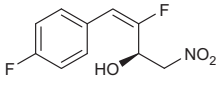
3g, 82% yield, 86% ee



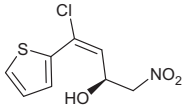
3h, 72% yield, 82% ee



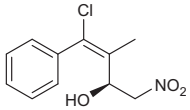
3i, 78% yield, 93% ee



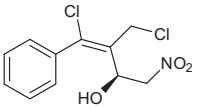
3j, 84% yield, 76% ee



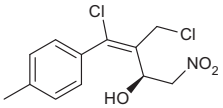
3k, 90% yield, 88% ee



3l, 73% yield, 98% ee



3m, 68% yield, 97% ee



3n, 65% yield, 97% ee

[a] Reactions were carried out on a 0.5 mmol scale of haloenals with 20 equiv of nitromethane in a mixture of 2.0 mL of THF, 5 mol % of ligand **L1** and 5 mol % of $Cu(OAc)_2 \cdot H_2O$ in the presence of 1.0 equiv of 4-methylmorpholine at −20 °C.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] The reaction time for **1a**–**f** was 48 h, for **1h**–**n** was 96 h.

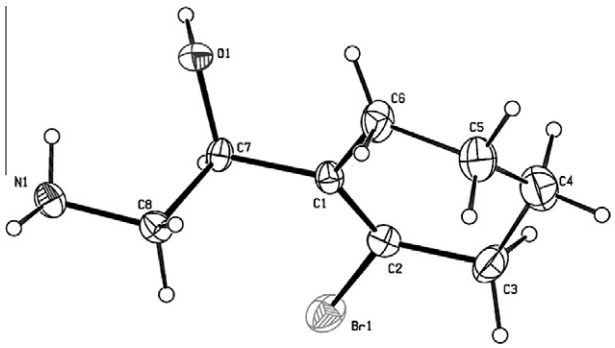
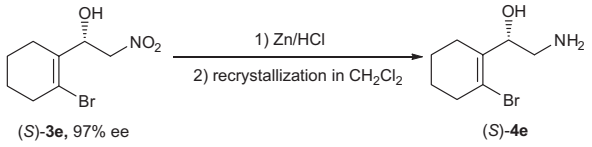


Figure 1. X-ray structure analysis of (*S*)-**4e**.[12]

results are in agreement with our previous observations,[3d] which revealed that the nitronate would attack the aldehyde from the *re* face when **L1** was used. Therefore, the absolute configuration of **4e** was assigned as (*S*) (Scheme 2).



(*S*)-**3e**, 97% ee (*S*)-**4e**

Scheme 2. The derivative of (*S*)-**3e**.

3. Conclusion

In conclusion, we have developed a highly chemoselective and enantioselective nitroaldol reaction between α- or β-haloenals and nitromethane by treatment of 5 mol % of **L1**–$Cu(OAc)_2 \cdot H_2O$ under mild reaction conditions. The reaction not only provides a wide variety of new β-nitroalcohol compounds in high to excellent yields (up to 94%) with excellent enantioselectivities (up to 99% ee), but also provides a new method to construct functionalized allylic alcohols. Further applications of this methodology are currently underway in our laboratory.

4. Experimental

4.1. General

Solvents were purified according to standard procedures and distilled before use. Reagents and starting materials purchased from commercial suppliers were used without further purification unless otherwise stated. For thin-layer chromatography (TLC), silica gel plates GF254 were used and compounds were visualized by irradiation with UV light, I_2, or by treatment with basic $KMnO_4$. NMR spectra were measured on a 400 MHz spectrometer. ^1H NMR chemical shifts were reported in ppm with tetramethylsilane (TMS, δ 0 ppm) as the internal standard. Data for ^1H NMR are reported as follows: chemical shift (ppm), and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad). Data for ^{13}C NMR are reported as ppm. High resolution mass spectral analyses (HRMS) were measured using EI, ESI ionization. High performance liquid chromatography (HPLC) analysis was performed on chiral columns. Optical rotations were measured in the solvent indicated. Flash chromatography was carried out on silica gel 200–300 mesh. The molecular ion peak of acyclic β-hydroxy nitroalkanes **3g**–**n** could not be detected through the HRMS analyses, so two of them, **3g**, **3k**, were reduced by Zn/HCl to provide the β-hydroxy aminoalkanes **4g**, **4k**, which were detected by HRMS.

4.2. Preparation of substrates 1a–n

A variety of haloenals were synthesized according to the literature; **1a**–**c**,[13] **1d**–**f**,[14] **1g**–**h**,[15] **1i**,[16] **1j**,[17] **1k**–**n**.[15] The ^1H and ^{13}C NMR of the products were in agreement with the literature data.

4.3. Procedure for the catalytic enantioselective Henry reaction of haloenals with nitromethane 3

Ligand **L1** (6.0 mg, 0.0250 mmol, 5.0 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (5.0 mg, 0.0250 mmol, 5.0 mol %) were added to a test tube containing absolute THF (2 mL). The solution was stirred for 1 h to give a blue solution at room temperature. To the resulting solution, aldehyde **1** (0.5 mmol), nitromethane (5 mmol, 20 equiv), and *N*-methylmorpholine (54 μL, 0.5 mmol, 1.0 equiv) were added successively and the tube was introduced in a bath at the reaction temperature without special precautions to exclude moisture or air. After the indicated time, 180 μL of 3 M HCl aqueous were added, and the mixture was concentrated and purified directly by column chromatography on silica gel, eluting with petroleum ether and ethyl acetate to afford the corresponding product.

4.4. Procedure for the reduction of β-hydroxy nitroalkanes with Zn/HCl 4

Zinc powder (314 mg, 4.78 mmol) was added to a solution of **3** (0.100 mmol) in ethanol/H_2O (3.4:0.8 mL) followed by concentrated HCl (0.66 mL). The mixture was stirred at room temperature for 4 h. Aqueous saturated $NaHCO_3$ (10 mL) and water (10 mL) were added, and the mixture was extracted with EtOAc (3×25 mL). The organic phase was dried ($MgSO_4$), concentrated under reduced pressure, and the residue was concentrated and purified directly by column chromatography on silica gel, eluting with CH_2Cl_2 and CH_3OH to afford the corresponding product.

4.5. (*S*)-1-(2-Chlorocyclohex-1-enyl)-2-nitroethanol 3a

$[\alpha]_D^{25} = -8.7$ (*c* 1.1, $CHCl_3$); Colorless oil. ^1H NMR ($CDCl_3$ 400 MHz): δ 1.68 (m, 4H), 2.00 (dd, *J* = 15.6, 2.4 Hz, 1H), 2.29–2.48 (m, 3H), 2.71 (s, 1H), 4.33–4.64 (m, 2H), 5.53 (dd, *J* = 9.0, 3.7 Hz, 1H). ^{13}C NMR ($CDCl_3$ 100 MHz): δ 21.72 23.37, 24.65, 33.81, 68.47, 77.62, 130.09, 130.38. IR (film): 3461, 2938, 2886, 2863, 1718, 1658, 1556, 1509, 1434, 1378, 1058, 825, 668. HRMS (EI, *m*/*z*): calcd for $C_8H_{12}NO_3Cl$ (M^+), 205.0506, found 205.0503; HPLC (Chiralpak AD-H, Hexane–*i*-PrOH = 90: 10, flow rate: 0.5 mL/min, λ = 210 nm), t_{minor} = 16.3, t_{major} = 18.4, 99% ee.

4.6. (*S*)-1-(2-Chlorocyclopent-1-enyl)-2-nitroethanol 3b

$[\alpha]_D^{25} = -12.9$ (*c* 0.9, $CHCl_3$); Colorless oil. ^1H NMR ($CDCl_3$ 400 MHz): δ 1.92–2.09 (m, 2H), 2.29–2.42 (m, 1H), 2.61 (dd, *J* = 10.8, 4.6 Hz, 3H), 2.93 (s, 1H), 4.41 (dd, *J* = 13.1, 3.4 Hz, 1H), 4.54 (dd, *J* = 13.1, 9.5 Hz, 1H), 5.33 (dd, *J* = 9.4, 3.3 Hz, 1H). ^{13}C NMR ($CDCl_3$ 100 MHz): δ 20.58, 29.71, 37.97, 65.50, 77.77, 130.44, 133.44. IR (film): 3443, 2958, 2925, 2855, 1657, 1621, 1556, 1441, 1379, 1071, 888, 682. HRMS (EI, *m*/*z*): calcd for $C_7H_{10}NO_3Cl$ (M^+), 191.0349, found 191.0345; HPLC (Chiralpak AD-H, Hexane–*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 210 nm), t_{minor} = 17.6, t_{major} = 19.6, 99% ee.

4.7. (*S*)-1-(2-Chlorocyclohept-1-enyl)-2-nitroethanol 3c

$[\alpha]_D^{25} = -15.1$ (*c* 1.1, $CHCl_3$); Colorless oil. ^1H NMR ($CDCl_3$ 400 MHz): δ 1.68–1.45 (m, 4H), 1.81–1.69 (m, 2H), 2.41–2.24 (m, 2H), 2.62 (dd, *J* = 10.9, 3.5 Hz, 2H), 2.76 (s, 1H), 4.38 (qd, *J* = 12.9, 6.6 Hz, 2H), 5.52 (dd, *J* = 9.3, 3.8 Hz, 1H). ^{13}C NMR ($CDCl_3$ 100 MHz): δ 24.89, 26.24, 31.34, 38.97, 69.39, 77.48, 134.49, 134.82. IR (film): 3440, 2926, 2853, 1649, 1613, 1556, 1510, 1446, 1378, 1074, 892, 740. HRMS (EI, *m*/*z*): calcd for $C_9H_{14}NO_3Cl$ (M^+), 219.0662, found 219.0658; HPLC (Chiralpak AD-H, Hexane–*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 210 nm), t_{minor} = 16.7, t_{major} = 21.3, 96% ee.

4.8. (*S*)-1-(2-Bromocyclopent-1-enyl)-2-nitroethanol 3d

$[\alpha]_D^{25} = -11.2$ (*c* 1.0, $CHCl_3$); Pale yellow oil. ^1H NMR ($CDCl_3$ 400 MHz): δ 1.89–2.06 (m, 2H), 2.22–2.36 (m, 1H), 2.56 (dtd, *J* = 7.9, 6.0, 2.6 Hz, 1H), 2.94 (br, 1H), 2.62–2.74 (m, 2H), 4.41 (ddd, *J* = 13.1, 3.3, 1.4 Hz, 1H), 4.53 (ddd, *J* = 13.0, 9.5, 1.0 Hz, 1H), 5.30 (d, *J* = 9.4 Hz, 1H). ^{13}C NMR ($CDCl_3$ 100 MHz): δ 21.47, 30.18, 40.16, 67.01, 77.69, 120.29, 137.02. IR (film): 3442, 2958, 2926, 2855, 1657, 1621, 1557, 1441, 1380, 1071, 889. HRMS (EI, *m*/*z*): calcd for $C_7H_{10}NO_3Br$ (M^+), 234.9884, found 234.9879; HPLC (Chiralpak AD-H, Hexane–*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 210 nm), t_{minor} = 17.8, t_{major} = 19.1, 97% ee.

4.9. (*S*)-1-(2-Bromocyclohex-1-enyl)-2-nitroethanol 3e

$[\alpha]_D^{25} = -7.15$ (*c* 1.0, $CHCl_3$); Colorless oil. ^1H NMR ($CDCl_3$ 400 MHz): δ 1.80–1.58 (m, 4H), 2.10–1.93 (m, 1H), 2.43–2.29 (m, 1H), 2.61–2.45 (m, 2H), 2.81 (br, 1H), 4.46 (d, *J* = 6.1 Hz, 2H), 5.47 (t, *J* = 6.3 Hz, 1H). ^{13}C NMR ($CDCl_3$ 100 MHz): δ 24.32, 25.61, 21.77 36.62, 71.33, 77.56, 122.60, 132.72. IR (film): 3446, 2938, 2884, 2862, 1653, 1616, 1556, 1514, 1377, 1074, 753, 664. HRMS (EI, *m*/*z*): calcd for $C_8H_{12}NO_3Br$ (M^+), 249.0001, found 248.9997; HPLC (Chiralpak AD-H, Hexane–*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 210 nm), t_{minor} = 33.8, t_{major} = 37.0, 97% ee.

4.10. (*S*)-1-(2-Bromocyclohept-1-enyl)-2-nitroethanol 3f

$[\alpha]_D^{25} = -12.4$ (*c* 1.2, $CHCl_3$); Pale yellow oil. ^1H NMR ($CDCl_3$ 400 MHz): δ 1.39–1.63 (m, 4H), 1.65–1.85 (m, 2H), 2.21–2.45 (m, 2H), 2.72 (dd, *J* = 10.9, 3.5 Hz, 2H), 2.76 (s, 1H), 4.48 (qd, *J* = 12.9, 6.6 Hz, 2H), 5.55 (dd, *J* = 9.3, 3.8 Hz, 1H). ^{13}C NMR ($CDCl_3$ 100 MHz): δ 24.96, 26.04, 31.37, 41.45, 72.49, 77.37, 126.17, 137.92. IR (film): 3443, 2957, 2923, 2852, 1556, 1438, 1379, 1067, 886, 675. HRMS (EI, *m*/*z*): calcd for $C_9H_{14}NO_3Br$ (M^+), 263.0157, found 263.0156; HPLC

(Chiralpak AD-H, Hexane–*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 210 nm), t_{minor} = 17.0, t_{major} = 20.8, 99% ee.

4.11. (*S,Z*)-4-Bhloro-1-nitro-4-phenylbut-3-en-2-ol *Z*-3g

$[\alpha]_D^{25} = -22.8$ (*c* 0.9, $CHCl_3$); Yellow oil. ^1H NMR ($CDCl_3$ 400 MHz): δ 2.87 (br, 1H) 4.58 (qd, *J* = 13.4, 5.9 Hz, 2H), 5.46 (ddd, *J* = 8.4, 7.3, 3.3 Hz, 1H), 6.15 (d, *J* = 7.3 Hz, 1H), 7.35–7.45 (m, 3H), 7.54–7.66 (m, 2H). ^{13}C NMR ($CDCl_3$ 100 MHz): δ 67.38, 78.15, 123.51, 126.54, 128.52, 129.70, 136.14, 136.51. IR (film): 3395, 3060, 1636, 1554, 1513, 1493, 1446, 1337, 1076, 762, 692. HPLC (Chiralpak AD-H, Hexane–*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 27.0, t_{minor} = 29.7, 86% ee.

4.12. (*S,Z*)-4-Chloro-1-nitro-4-p-tolylbut-3-en-2-ol *Z*-3h

$[\alpha]_D^{25} = -25.6$ (*c* 0.9, $CHCl_3$); Yellow oil. ^1H NMR ($CDCl_3$ 400 MHz): δ 2.35 (s, 3H), 3.13 (br, 1H), 4.54 (dd, *J* = 11.3, 5.9 Hz, 2H), 5.33–5.55 (m, 1H), 6.10 (d, *J* = 7.3 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR ($CDCl_3$ 100 MHz): δ 21.09, 67.38, 78.23, 122.51, 126.38, 129.13, 133.31, 136.47, 139.86. IR (film): 3391, 3094, 2923, 1610, 1554, 1509, 1417, 1335, 1077, 816. HPLC (Chiralpak AS-H, Hexane–*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 29.7, t_{minor} = 35.6, 82% ee.

4.13. (*R,E*)-3-Bromo-1-nitro-4-phenylbut-3-en-2-ol *E*-3i

$[\alpha]_D^{25} = +19.8$ (*c* 1.0, $CHCl_3$); Pale yellow oil. ^1H NMR ($CDCl_3$ 400 MHz): δ 3.23 (s, 1H), 4.61 (dd, *J* = 13.1, 8.8 Hz, 1H), 4.72 (dd, *J* = 13.1, 3.4 Hz, 1H), 5.08 (d, *J* = 7.5 Hz, 1H), 7.31–7.42 (m, 3H), 7.56–7.65 (m, 2H). ^{13}C NMR ($CDCl_3$ 100 MHz): δ 74.08, 78.91, 121.54, 128.24, 128.76, 129.04, 130.83, 133.98. IR (film): 3049, 3057, 2966, 1636, 1598, 1555, 1493, 1446, 1378, 1076, 756, 692, 522. HPLC (Chiralpak OD-H, Hexane–*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 38.9, t_{minor} = 33.6, 93% ee.

4.14. (*R,E*)-3-Fluoro-4-(4-fluorophenyl)-1-nitrobut-3-en-2-ol *E*-3j

$[\alpha]_D^{25} = +33.6$ (*c* 1.0, $CHCl_3$); Yellow oil. ^1H NMR ($CDCl_3$ 400 MHz): δ 3.26 (s, 1H), 4.66 (qd, *J* = 13.5, 6.0 Hz, 2H), 4.95–5.13 (m, 1H), 5.97 (d, *J* = 39.4 Hz, 1H), 6.99–7.10 (m, 2H), 7.43–7.53 (m, 2H). ^{13}C NMR ($CDCl_3$ 100 MHz): δ 67.65, 67.98, 77.57, 107.55, 107.60, 115.49, 115.71, 127.78, 127.81, 127.84, 130.57, 130.65, 130.73, 153.24, 153.26, 155.89, 155.91, 160.95, 160.99, 163.42, 163.46. ^{19}F NMR (376 MHz, CDCl3): δ −119.72, −119.70, −119.62, −119.59, −112.59, −112.57. IR (film): 3080, 3063, 2975, 1646, 1500, 1555, 1473, 1461, 1378, 1243, 1150, 1110, 756, 682. HPLC (Chiralpak AD-H, Hexane–*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 41.0, t_{minor} = 44.9, 76% ee.

4.15. (*S,E*)-4-Chloro-1-nitro-4-(thiophen-2-yl)but-3-en-2-ol *E*-3k

$[\alpha]_D^{25} = -30.35$ (*c* 1.1, $CHCl_3$); Red oil. ^1H NMR ($CDCl_3$ 400 MHz): δ 2.98 (s, 1H), 4.38–4.78 (m, 2H), 5.42 (td, *J* = 7.7, 4.0 Hz, 1H), 6.11 (d, *J* = 7.5 Hz, 1H), 7.00 (dd, *J* = 5.0, 3.8 Hz, 1H), 7.20–7.42 (m, 2H). ^{13}C NMR ($CDCl_3$ 100 MHz): δ 67.02, 78.20, 121.28, 127.20, 127.33, 127.56, 129.76, 139.78. IR (film): 3405, 3070, 2956, 1611, 1555, 1498, 1417, 1331, 1081, 814, 712. HPLC (Chiralpak AS-H, Hexane–*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 37.9, t_{minor} = 47.3, 88% ee.

4.16. (*S,E*)-4-Chloro-3-methyl-1-nitro-4-phenylbut-3-en-2-ol *E*-3l

$[\alpha]_D^{25} = -50.05$ (*c* 1.0, $CHCl_3$); Yellow oil. ^1H NMR ($CDCl_3$ 400 MHz): δ 2.56 (br, 1H), 2.01 (s, 3H), 4.34 (dd, *J* = 13.0, 3.4 Hz, 1H), 4.54 (dd, *J* = 13.0, 9.5 Hz, 1H), 5.02 (dd, *J* = 9.5, 3.3 Hz, 1H), 7.21–7.32 (m, 2H), 7.35–7.46 (m, 3H). ^{13}C NMR ($CDCl_3$ 100 MHz): δ 14.02, 68.58, 78.33, 128.34, 128.46, 128.76, 128.90, 129.11, 130.67, 133.27, 137.30. IR (film): 3402, 3045, 2996, 2934, 1615, 1567, 1536, 1489, 1379, 1108, 745. HPLC (Chiralpak AS-H, Hexane–*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 23.6, t_{minor} = 41.7, 98% ee.

4.17. (*S,Z*)-4-Chloro-3-(chloromethyl)-1-nitro-4-phenylbut-3-en-2-ol *Z*-3m

$[\alpha]_D^{25} = -141.15$ (*c* 1.0, $CHCl_3$); Yellow oil. ^1H NMR ($CDCl_3$ 400 MHz): δ 2.95 (d, *J* = 3.4 Hz, 1H), 4.43–4.46 (m, 1H), 4.47 (d, *J* = 2.5 Hz, 1H), 4.58 (d, *J* = 11.3 Hz, 1H), 4.80 (dd, *J* = 13.7, 10.2 Hz, 1H), 5.12 (d, *J* = 10.2 Hz, 1H), 7.30–7.35 (m, 2H), 7.42–7.46 (m, 4H). ^{13}C NMR ($CDCl_3$ 100 MHz): δ 39.00, 67.87, 78.57, 128.06, 128.92, 129.89, 131.23, 136.14, 139.51. IR (film): 3395, 3061, 2924, 1595, 1556, 1516, 1489, 1378, 1077, 767, 700. HPLC (Chiralpak AS-H, Hexane–*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 27.0, t_{minor} = 30.4, 97% ee.

4.18. (*S,Z*)-4-Chloro-3-(chloromethyl)-1-nitro-4-*p*-tolylbut-3-en-2-ol *Z*-3n

$[\alpha]_D^{25} = -206.3$ (*c* 1.2, $CHCl_3$); Yellow oil; ^1H NMR ($CDCl_3$ 400 MHz): δ 2.95 (d, *J* = 3.4 Hz, 3H), 4.44 (dd, *J* = 6.8, 4.3 Hz, 1H), 4.46–4.51 (m, 2H), 4.58 (dd, *J* = 11.3, 0.4 Hz, 1H), 4.80 (dd, *J* = 13.7, 10.2 Hz, 1H), 5.12 (d, *J* = 10.2 Hz, 1H), 7.21–7.26 (m, 4H). ^{13}C NMR (CD_3COCD_3 100 MHz): δ 14.92, 39.13, 40.38, 67.83, 78.50, 125.74, 128.46, 131.03, 132.16, 139.26, 141.49. IR (film): 3438, 3033, 2956, 2922, 2852, 1630, 1591, 1552, 1489, 1422, 1380, 1088, 820. HPLC (Chiralpak AS-H, Hexane–*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 210 nm), t_{major} = 46.0, t_{minor} = 71.9, 97% ee.

4.19. (*S*)-2-Amino-1-(2-bromocyclohex-1-enyl)ethanol 4e

$[\alpha]_D^{25} = +14.05$ (*c* 0.23, $CHCl_3$); White solid, mp: 114–116 °C; ^1H NMR (CD_3COCD_3 400 MHz): δ 1.59–1.78 (m, 4H), 2.01–2.13 (m, 4H), 2.20–2.34 (m, 1H), 2.47 (dt, *J* = 6.5, 2.7 Hz, 2H), 2.76 (dd, *J* = 11.9, 7.3 Hz, 1H), 3.32 (dd, *J* = 11.9, 6.8 Hz, 1H), 4.78 (t, *J* = 7.0 Hz, 1H). ^{13}C NMR (CD_3COCD_3 100 MHz): δ22.82, 25.43, 26.74, 37.56, 50.81, 79.83, 119.51, 137.41. HRMS (ESI, *m*/*z*): calcd for $C_8H_{15}NOBr$ ($[M+H]^+$), 220.0332, found 220.0332.

4.20. (*Z*)-1-Amino-4-chloro-4-phenylbut-3-en-2-ol *Z*-4g

Thick oil; ^1H NMR ($CDCl_3$ 400 MHz): δ 2.62 (br, 3H), 2.80 (dd, *J* = 12.8, 8.1 Hz, 1H), 2.98 (d, *J* = 12.8 Hz, 1H), 4.71 (td, *J* = 7.8, 3.8 Hz, 1H), 6.20 (d, *J* = 7.5 Hz, 1H), 7.33–7.38 (m, 3H), 7.60 (m, 2H). ^{13}C NMR ($CDCl_3$ 100 MHz): δ 46.15, 70.55, 126.51, 128.09, 128.37, 128.99, 134.21, 137.23. HRMS (ESI, *m*/*z*): calcd for $C_{10}H_{13}NOCl$ ($[M+H]^+$), 198.0680, found 198.0678.

4.21. (*E*)-1-Amino-4-chloro-4-(thiophen-2-yl)but-3-en-2-ol *E*-4k

Thick red oil; ^1H NMR ($CDCl_3$ 400 MHz): δ 2.79 (dd, *J* = 12.9, 8.2 Hz, 1H), 2.90 (dd, *J* = 12.9, 3.6 Hz, 1H), 3.66 (br, 3H), 4.67 (td, *J* = 7.9, 3.9 Hz, 1H), 6.15 (d, *J* = 7.7 Hz, 1H), 6.93 (ddd, *J* = 5.2, 2.7, 1.1 Hz, 1H), 7.17–7.21 (m, 1H), 7.23 (dd, *J* = 2.4, 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$ 100 MHz): δ 45.95 69.68, 126.14, 126.23, 126.44, 127.38, 127.46, 140.97. HRMS (ESI, *m*/*z*): calcd for $C_8H_{11}NOSCl$ ($[M+H]^+$), 204.0244, found 204.0239;

Acknowledgments

This work was financially supported by grants from National Science Foundation of China (Nos. 21172082 and 20872041). The Center of Analysis and Testing of Huazhong University of Science and Technology is gratefully acknowledged for characterization of the new compounds.

References

1. (a) Bandini, M.; Piccinelli, F.; Tommasi, S.; Umani-Ronchi, A.; Ventrici, C. *Chem. Commun.* **2007**, 616–618; (b) Trost, B. M.; Yeh, V. S. C.; Ito, H.; Bremeyer, N. *Org. Lett.* **2002**, *4*, 2621–2623; (c) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001; (d) Shibasaki, M.; Gröer, H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. III, pp 1075–1090; (e) Rosini, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 2, pp 321–340.
2. For recent reviews on the catalytic asymmetric Henry reaction, see: (a) Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, 2561–2574; (b) Boruwa, J.; Gogoi, N.; Saikia, P. P.; Barua, N. *Tetrahedron: Asymmetry* **2006**, *17*, 3315–3326; (c) Palomo, C.; Oiarbide, M.; Mielgo, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5442–5444.
3. For recent examples of asymmetric Henry reactions: (a) Zhou, Y.; Gong, Y. *Eur. J. Org. Chem.* **2011**, *76*, 6092–6099; (b) Maggi, R.; Lanari, D.; Oro, C.; Sartori, G.; Vaccaro, L. *Eur. J. Org. Chem.* **2011**, 5551–5554; (c) Gualandi, A.; Cerisoli, L.; Stoeckli-Evans, H.; Savoia, D. *J. Org. Chem.* **2011**, *76*, 3399–3408; (d) Zhou, Y.; Dong, J.; Zhang, F.; Gong, Y. *J. Org. Chem.* **2011**, *76*, 588–600; (e) Dhahagani, K.; Rajesh, J.; Kannan, R.; Rajagopal, G. *Tetrahedron: Asymmetry* **2011**, *22*, 857–865; (f) Reddy, B. V. S.; Reddy, S. M.; Manisha, S.; Madan, C. *Tetrahedron: Asymmetry* **2011**, *22*, 530–535; (g) Guo, Z.-L.; Zhong, S.; Li, Y.-B.; Lu, G. *Tetrahedron: Asymmetry* **2011**, *22*, 238–245; (h) Wei, Y.; Yao, L.; Zhang, B.; He, W.; Zhang, S. *Tetrahedron* **2011**, *67*, 8552–8558; (i) Xin, D.; Ma, Y.; He, F. *Tetrahedron: Asymmetry* **2010**, *21*, 333–338; (j) Steurer, M.; Bolm, C. *J. Org. Chem.* **2010**, *75*, 3301–3310; (k) Noole, A.; Lippur, K.; Metsala, A.; Lopp, M.; Kanger, T. *J. Org. Chem.* **2010**, *75*, 1313–1316; (l) Yang, W.; Liu, H.; Du, D.-M. *Org. Biomol. Chem.* **2010**, *8*, 2956–2960; (m) Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692–12693; (n) Trost, B. M.; Yeh, V. S. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 861–863; (o) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418–4420.
4. (a) Takahashi, H.; Yoshida, K.; Yanagisawa, A. *J. Org. Chem.* **2009**, *74*, 3632–3640; (b) Samanta, K.; Kar, G. K.; Sarkar, A. K. *Tetrahedron Lett.* **2008**, *49*, 1461–1464; (c) Some, S.; Dutta, B.; Ray, J. K. *Tetrahedron Lett.* **2006**, *47*, 1221–1224; (d) Banwell, M. G.; Lupton, D. W.; Ma, X.; Renner, J.; Sydnes, M. O. *Org. Lett.* **2004**, *6*, 2471–2474; (e) Cho, C. S.; Lim, D. K.; Heo, N. H.; Kim, T.; Shim, S. C. *Chem. Commun.* **2004**, 104–105.
5. (a) Mal, S. K.; Ray, D.; Ray, J. K. *Synlett* **2005**, 2135–2140; (b) Mal, S. K.; Ray, D.; Ray, J. K. *Tetrahedron Lett.* **2004**, *45*, 277–279.
6. (a) Yao, W.; Wu, Y.; Wang, G.; Zhang, Y.; Ma, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 9713–9716; (b) Zhang, J.; Gong, Y. *Org. Lett.* **2011**, *13*, 176–179.
7. Yasmin, N.; Ray, J. K. *Synlett* **2010**, 0924–0930.
8. (a) Shimizu, M.; Goto, H.; Hayakawa, R. *Org. Lett.* **2002**, *2*, 4097–4099; (b) Cho, C. S.; Kim, J. U.; Choi, H. J. *J. Organomet. Chem.* **2008**, *693*, 3677–3680.
9. Cho, C. S.; Kima, H. B.; Ren, W. X.; Yoon, N. S. *Appl. Organomet. Chem.* **2010**, *24*, 817–820.
10. For seminal studies on the DBU-prompted Morita-Baylis–Hillman reaction, see: (a) Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311–2312; For a review on ammonium enolates, see: (b) Gaunt, M. J.; Johansson, C. C. C. *Chem. Rev.* **2007**, *107*, 5596–5605.
11. (a) Parker, K. A.; Fokas, D. *J. Org. Chem.* **2006**, *71*, 449–455; (b) Sousa, S. E.; O'Brien, P.; Pilgram, C. D. *Tetrahedron Lett.* **2001**, *42*, 8081–8083; (c) Lu, X.; Zhu, G.; Wang, Z. *Synlett* **1998**, 115–121; (d) Corey, E. J.; Guzman-Perez, A.; Lazerwith, S. E. *J. Am. Chem. Soc.* **1997**, *119*, 11769–11776; (e) Kazmaier, U.; Schneider, C. *Synlett* **1996**, 975–977.
12. The data for X-ray crystal analysis of (*S*)-**4e** has been deposited at the CCDC (No. 853950).
13. Gelalcha, F. G.; Schulze, B. *J. Org. Chem.* **2002**, *67*, 8400–8406.
14. Jana, R.; Paul, S.; Biswas, A.; Ray, J. K. *Tetrahedron Lett.* **2010**, *51*, 273–276.
15. Shaffer, A. R.; Schmidt, J. A. R. *Chem. Eur. J.* **2009**, *15*, 2662–2673.
16. Bovonsombat, P.; Rujiwarangkul, R.; Bowornkiengkai, T.; Leykajarakul, J. *Tetrahedron Lett.* **2007**, *48*, 8607–8610.
17. Luo, F.; Wang, P.; Gong, Y. *Tetrahedron Lett.* **2010**, *51*, 1693–1695.