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Highly enantioselective Henry reaction catalyzed by a new chiral C_2-symmetric *N,N′*-bis(isobornyl)ethylenediamine–copper complex

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ABSTRACT

A new chiral C_2-symmetric *N,N′*-bis(isobornyl)ethylenediamine–copper complex is found to be an efficient catalyst in the enantioselective Henry reaction between nitromethane and various aldehydes to provide β-hydroxy nitroalkanes with high chemical yield (up to 95%) and high enantiomeric excess (up to 90%).

1. Introduction

The nitroaldol (Henry) reaction is a powerful atom economical C–C bond forming reaction as the resulting β-hydroxy nitroalkanols can be transformed into valuable building blocks.[1] The first catalytic asymmetric version of this reaction was reported using lanthanide–BINOL complexes which yielded products with ⩽90% ee.[2] Later, copper-based bisoxazoline complexes were reported to give products with 90–92% ee,[3] and a chiral dinuclear zinc complex was reported to yield the products with 93% ee.[4] In addition, several other chiral metal complexes,[5] Bronsted bases such as guanidine bases,[6] and cinchona alkaloids[7] have been reported to promote the asymmetric Henry reaction with high enantioselectivities. Some of these catalytic systems have limitations such as lower substrate scope, being limited to aromatic aldehydes or aliphatic aldehydes, requirement of low reaction temperatures, the need for organic bases and 4 Å molecular sieves as additives, and relatively high catalyst loading. Therefore, there has been sustained interest in the development of new catalyst systems for catalytic enantioselective Henry reaction variants. Although several chiral metal complexes have been reported to control the stereochemical outcomes of this transformation, copper-based asymmetric catalysts are particularly promising due to their high catalytic activity.[8]

The copper complexes prepared from naturally occurring D-(+) camphor-based ligands **1a**,[8c] **1b**,[8k] **1c**,[8m] and **1d**[8m] gave up to 67–98% ee in the asymmetric Henry reaction between nitromethane and aldehydes (Fig. 1).

Whereas the synthesis of diamine derivatives **1c** and **1d** requires multiple step procedures starting from D-(+)-camphor, the synthesis of **1a** and **1b** requires the somewhat expensive aminomethyl pyridine. Herein, we report an enantioselective Henry reaction catalyzed by a new readily accessible chiral C_2-symmetric *N,N′*-bis(isobornyl)ethylenediamine **4**–$Cu(OAc)_2 \cdot H_2O$ complex.

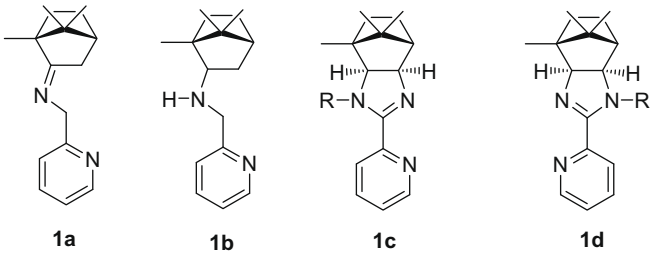

Figure 1.

2. Results and discussion

During our research toward the synthesis and resolution of C_2-symmetrical chiral diamines and amino alcohols,[9] we became interested in the chiral diamines readily accessible from natural sources. Previously, we have reported a modified procedure for the synthesis of isobornylaniline[10a,b] and its application in the mechanistic investigation of the hydroboration reaction.[10c] The C_2-symmetric camphor diimine molecule can be readily accessed following a simple protocol using D(+)-camphor and ethylene diamine (Scheme 1).[10a,b,d]

We have examined the use of the ligands **3** and **4** in metal complexes for use in the asymmetric Henry reaction. The reaction of ligand **3** with $Cu(OAc)_2 \cdot H_2O$ in dichloromethane solvent followed by reaction with nitromethane and 4-nitrobenzaldehyde, afforded the nitroaldol product in 36% ee (90% yield). Encouraged by the catalytic activity of this diimine copper complex, we have further investigated the transformation using the corresponding *N,N′*-bis(isobornyl)ethylenediamine ligand **4** (i.e., *N,N′*-bis[(1*R*,2*R*,4*R*)-

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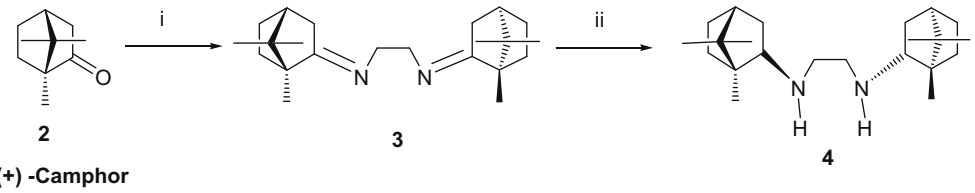


Scheme 1. Reagents and conditions: (i) ethylenediamine (0.50 equiv), $BF_3{\cdot}Et_2O$ (1–5 mol %), PhMe, reflux (Dean–Stark), 12 h; (ii) $NiCl_2$ (2.1 equiv), $NaBH_4$ (3.0 equiv), MeOH, −40 °C→rt, 12 h.

1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1,2-ethanediamine). A series of divalent Lewis acids in combination with chiral bidentate ligand **4** were screened as catalysts for the nitroaldol reaction between nitromethane and 4-nitrobenzaldehyde in isopropanol solvent. The results are summarized in Table 1. The enantiomeric excess of 50% was obtained using the $Cu(OAc)_2{\cdot}H_2O$ (Scheme 2). Some other metal acetates are capable of producing good chemical yield but the enantiomeric purities were poor (Table 1). Accordingly, we have performed the reactions of the copper complex derived from ligand **4** with $Cu(OAc)_2{\cdot}H_2O$ in isopropanol solvent using different amounts of the ligand **4** and copper(II) reagent (1, 5, and 10 mol %). The enantiomeric excess obtained was still low, 40%, 40%, and 50% ee, respectively.

Table 1
Enantioselective Henry reaction of nitromethane with 4-nitrobenzaldehyde using different metal complexes with ligand **4**[a]

S.no.	Metal acetate	Time (h)	Yield[b] (%)	ee[c] (%)
1	$Zn(OAc)_2{\cdot}2H_2O$	0.75	70	2
2	$Ni(OAc)_2{\cdot}4H_2O$	0.50	85	5
3	$Mn(OAc)_2{\cdot}2H_2O$	0.50	75	0
4	$Cu(OAc)_2{\cdot}H_2O$	0.50	90	50
5	$Cu(OTf)_2$	13	80	6

[a] In this reaction, ligand **4** (0.12 mm) and Lewis acid (0.10 mm) were stirred for 3 h in isopropanol (1 mL) for complex formation. All the reactions were carried out using 4-nitrobenzaldehyde (1.0 mm), 1 mL of isopropanol, and 10.0 mmol of nitromethane at 25 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis (Chiralcel OD-H).

We then examined the effect of different solvents (Table 2). The use of the aprotic solvent dichloromethane gave 60% ee. When the copper complex was prepared in CH_2Cl_2 (1 mL) and the Henry reaction was carried out after the addition of isopropanol (1 mL), the enantiomeric excess obtained was the same (60% ee). When the copper complex **5** (Fig. 2)[11] was formed in dichloromethane and isopropanol was added after removal of CH_2Cl_2, the reaction gave higher selectivity, 74% ee (Table 2, entry 4). The reactions in alcoholic solvents are superior to aprotic solvents. It was found that the enantioselectivity increased in the order MeOH < EtOH < *n*-PrOH < *i*-PrOH, but in the case of *t*-BuOH the ee decreased, while the use of 10 equiv of nitromethane was found to be sufficient for the completion of the reaction (Scheme 3).

The reaction can be performed with lower catalyst loading (1 mol %, Table 3) but using 10 mol % of the ligand **4** and $Cu(OAc)_2{\cdot}H_2O$, the reaction can be completed in 0.5 h at 25 °C (Table 3, entry 3).

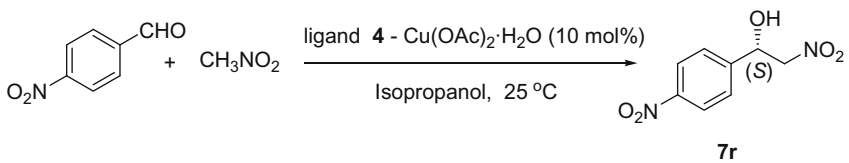
Table 2
Effect of solvent on the enantioselective Henry reaction between nitromethane and 4-nitrobenzaldehyde using complex **5**[a]

Entry	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	MeOH	0.50	90	62
2	EtOH	0.50	88	60
3	*n*-PrOH	0.50	92	68
4	*i*-PrOH	0.50	95	74
5	*t*-BuOH	0.50	90	30
6	CH_2Cl_2	20	53	60
7	MeCN	12	70	20
8	Toluene	24	50	60
9	CH_2Cl_2 + *i*-PrOH	1	85	60
10	THF	12	80	54

[a] The ligand **4** (0.12 mm) and $Cu(OAc)_2{\cdot}H_2O$ (0.10) in CH_2Cl_2 were stirred for 6 h for complex formation and the CH_2Cl_2 was removed under reduced pressure. All reactions were run using 1.0 mmol of 4-nitrobenzaldehyde in 1 mL of isopropanol and 10.0 mmol of nitromethane at 25 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis (Chiralcel OD-H).

In order to examine the scope of this transformation, experiments were carried using several substrates (Table 4). A variety of aldehydes provided nitroaldol products with enantiomeric excesses in the range of 64–90% at 25 °C (Table 4, Scheme 4). Furthermore, aliphatic aldehydes were smoothly converted to nitroaldols in good yields with high enantioselectivity (up to 88% ee). Aldehydes containing either electron-withdrawing or electron-donating substituents at various positions of the aromatic ring of aryl aldehydes gave products with ees ranging from 64% to 90% ee (Table 4). In some cases, along with the expected nitroaldol product, small amounts (5–10%) of the corresponding elimination product were also obtained (Table 4, entry 19). The reaction of *o*-methoxy benzaldehyde provided the corresponding adduct with 75% yield and 90% ee (Table 4, entry 2).The biologically active norphenylephrine precursor 1-(3-hydroxyphenyl)-2-nitroethanol was obtained with 80% ee and 72% yield (Table 4, entry 19).[8i]

The results may be rationalized by the transition state model as shown in Figure 3. The reaction probably involves Cu-mediated dual activation of the nitronate and the aldehyde substrates. In the favorable transition state, the nucleophilic carbon of the nitronate ion formed in situ by deprotonation of nitromethane with an acetate ion approaches the aldehyde from the *Si* face to give the (*S*)-isomer as the major product. *Re* face attack is not favored due to severe non-bonding interactions between the aromatic group or longer chain of the corresponding aldehyde with the methyl substituents of the C_2-symmetric *N,N′*-bis(isobornyl)ethylenediamine ligand **4**.



Scheme 2.

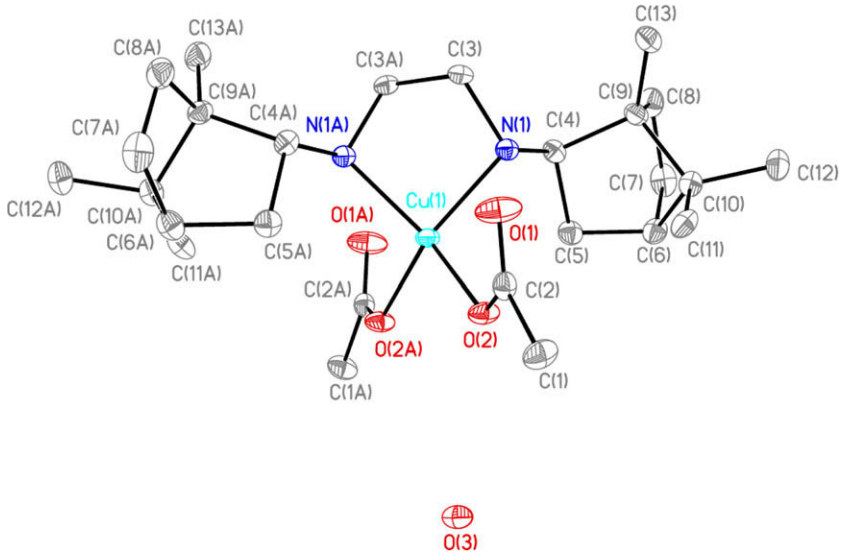
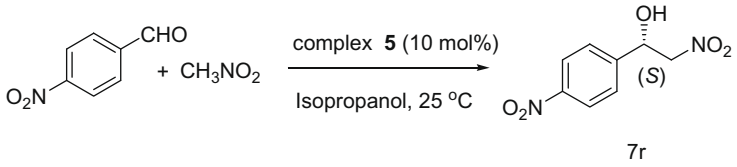


Figure 2. ORTEP representation of the *N*,*N*′-bis(isobornyl)ethylenediamine–Cu(OAc)$_2$·H$_2$O complex **5** (all the H-atoms were removed for clarity and thermal ellipsoids were drawn with 25% probability).



Scheme 3.

Table 3
Effect of quantities of the complex **5**[a]

Entry	mol %	Time (h)	Yield[b] (%)	ee[c] (%)
1	1	2	60	72
2	5	0.75	70	72
3	10	0.50	95	74
4	15	0.50	92	58
5	20	0.50	91	40
6	30	0.50	93	30

[a] Ligand **4** (0.012, 0.052, 0.12, 0.17, 0.22, and 0.30 mmol) and Cu(OAc)$_2$·H$_2$O (0.010, 0.050, 0.10, 0.15, 0.20, and 0.30 mmol) in CH_2Cl_2 were stirred for 6 h for complex formation and the CH_2Cl_2 was removed under reduced pressure. All reactions were run using 1.0 mmol of 4-nitrobenzaldehyde in 1 mL of isopropanol and 10.0 mmol of nitromethane at 25 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis (Chiralcel OD-H).

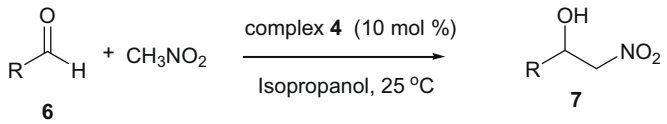
3. Conclusion

In summary, the readily accessible new class of C_2-symmetrical *N*,*N*′-bis(isobornyl)ethylenediamine ligand **4** is useful in the preparation of copper complex **5** from Cu(OAc)$_2$·H$_2$O in CH_2Cl_2. The Henry reaction using this copper complex **5** in isopropanol at 25 °C gave the adducts in high yields and with good enantioselectivity. In addition, the present procedure for the Henry reaction has several advantages including air-tolerance, relatively short reaction times, and high stereochemical control with a wide range of substrates. The β-hydroxy nitroalkanols derivatives are very useful intermediates in the synthesis of β-receptor agonists (−)-denopamine, (−)-arbutamine,[12] the β-blockers (*S*)-metoprolol, (*S*)-propanolol, and (*S*)-pindolol.[13a–c] Also, the nitroaldols are useful in the synthesis of pharmacologically important β-amino alcohol derivatives, such as chloramphenicol, ephedrine, and sphingosine.[14a,b] Therefore, the results described here have significant potential for further synthetic exploitation.

Table 4
Enantioselective Henry reaction of various aldehydes with nitromethane catalyzed by complex **5**[a]

Entry	Substrate (**6**)	Time (h)	Product (**7**)	Yield[b] (%)	ee[c] (%)
1	Ph–	11	**7a**	70	84 (*S*)
2	*o*-MeO–C$_6$H$_4$	13	**7b**	75	90 (*S*)
3	*m*-MeO–C$_6$H$_4$	12	**7c**	80	88 (*S*)
4	*m*-Me–C$_6$H$_4$	12	**7d**	85	88 (*S*)
5	*p*-Me–C$_6$H$_4$	24	**7e**	60	78 (*S*)
6	*o*-Cl–C$_6$H$_4$	7	**7f**	70	86 (*S*)
7	*m*-Cl–C$_6$H$_4$	15	**7g**	75	78
8	*p*-Cl–C$_6$H$_4$	24	**7h**	60	68 (*S*)
9	*o*-Br–C$_6$H$_4$	15	**7i**	75	70
10	*m*-Br–C$_6$H$_4$	12	**7j**	78	64
11	*p*-Br–C$_6$H$_4$	16	**7k**	70	86 (*S*)
12	*p*-F–C$_6$H$_4$	4	**7l**	80	82 (*S*)
13	1-Naphthyl	12	**7m**	72	72 (*S*)
14	2-Naphthyl	12	**7n**	70	82 (*S*)
15	2-Furfuryl	13	**7o**	81	88 (*S*)
16	*o*-NO$_2$–C$_6$H$_4$	0.5	**7p**	83	84 (*S*)
17	*m*-NO$_2$–C$_6$H$_4$	0.5	**7q**	85	78 (*S*)
18	*p*-NO$_2$–C$_6$H$_4$	0.5	**7r**	95	74 (*S*)
19	*m*-OH–C$_6$H$_4$	15	**7s**	72	80
20	Cyclohexyl	7	**7t**	90	88 (*S*)
21	Isopropyl	8	**7u**	90	86 (*S*)
22	Isobutyl	10	**7v**	90	88 (*S*)

[a] The ligand **4** (0.12) and Cu(OAc)$_2$·H$_2$O (0.10) in CH_2Cl_2 were stirred for 6 h for complex formation and the CH_2Cl_2 was removed under reduced pressure. All reactions were run using the aldehydes (1 mm) in 1 mL of isopropanol and 10.0 mmol of nitromethane at 25 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis (Chiralcel OD-H, AD-H, and OJ-H).



Scheme 4.

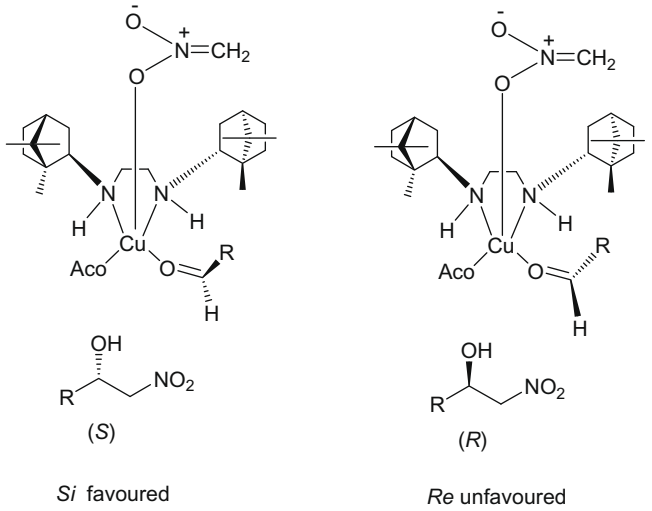


Figure 3. Stereochemical model.

4. Experimental section

Infrared spectra were recorded on JASCO FT-IR spectrophotometer Model 5300. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AV-400 spectrometers with chloroform-*d* as a solvent and TMS as the reference (δ = 0 ppm). Coupling constants *J* are in hertz. Elemental analyses were carried out on a Flash EA 1112 series analyzer. Optical rotations were measured in an AUTOPOL-IV automatic polarimeter (readability ±0.001). Chromatography was carried out using Acme's silica gel (100–200 mesh and 230–400 mesh). The solvents were dried using the standard procedures. The reagents were used commercially after further distillation.

4.1. General procedure for the preparation of ligand 3

An oven-dried 50 mL reaction flask was flushed with dry nitrogen, and (D)-(+)-camphor (1.52 g, 10 mmol) and ethylene diamine (300 mg,5 mmol) were taken in 20 mL toluene. BF_3:OEt_2 (5 mol %) was added and the contents were refluxed for 12 h using a Dean–Stark apparatus. The diastereomerically pure (E,E)-bis(camphorylidene)ethylenediimine **3** was obtained in almost quantitative yield. The reduction of **3** in the presence of nickel boride[10a,b,d] (in situ generated from anhydrous $NiCl_2$ (2 equiv) and $NaBH_4$ (3 equiv) in methanol at −40 °C to rt, 12 h) resulted in 90% yield of diamine **4** with 95:5 *exo*:*exo* selectivity. This mixture isolated as dihydrochloride, could be readily enriched to 100% diastereomeric purity by simple recrystallization from ethanol in excellent recovery (83% yield) of **4**.

4.2. Data for the *N,N*′-bis(isobornyl)ethylenediamine 4

85% Yield, white solid; $[\alpha]_D^{25} = -107.6$ (*c* 0.42, EtOH), [lit. $[\alpha]_D^{20} = -107.7$ (*c* 0.65, EtOH, 99% ee)];[10d] IR ν_{max}/cm^{-1} (KBr): 3435, 3032, 2920, 1552, 1379, 1066; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.65–2.64 (m, 2H), 2.52–2.49 (m, 4H), 1.67–1.49 (m, 8H),1.06–1.04 (m, 6H), 0.99 (s, 6H), 0.86 (s, 6H), 0.80 (s, 6H). ^{13}C (100 MHz, $CDCl_3$) δ 66.7, 48.3, 48.2, 46.6, 45.2, 39.0, 36.9, 27.3, 20.6, 20.5, 12.2.

4.3. General procedure for the enantioselective Henry reaction

To an oven-dried 10 mL round-bottomed flask, a solution of ligand **4** (39.0 mg, 0.12 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (20.0 mg, 0.10 mmol) in the CH_2Cl_2 solvent (1 mL) was stirred for 6 h at 25 °C. A clear deep blue solution resulted. The CH_2Cl_2 was removed under reduced pressure and isopropanol (1 mL) and nitromethane (10 mmol) were added and stirred for 30 min. The aldehyde (1 mmol) was added and the reaction mixture was stirred at 25 °C until the reaction was complete (disappearance of aldehyde by TLC). After evaporation of the solvent, the residue was purified by column chromatography on silica gel (10–15% EtOAc–hexane) to afford the nitroaldol product.

4.4. General procedure for the preparation of copper complex 5 crystals

To an oven-dried 25 mL round-bottomed flask, a solution of ligand **4** (2.1 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol) in the CH_2Cl_2 solvent (20 mL) was added and stirred for 6 h at 25 °C. The resulting blue solution in CH_2Cl_2 was left until most of the solvent evaporated. The crystals obtained were suitable for single crystal X-ray structural analysis.

4.4.1. (*S*)-1-Phenyl-2-nitroethanol 7a

70% Yield, 84% ee, colorless oil; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85:15 *v*/*v*, 0.8 mL/min, 23 °C, UV 215 nm): $t_{R(minor)}$ = 11.9 min, $t_{R(major)}$ = 14.1 min; $[\alpha]_D^{25} = +32.6$ (*c* 0.42, CH_2Cl_2, 84% ee), [lit. $[\alpha]_D^{25} = +36.8$ (*c* 4.04, CH_2Cl_2, 95% ee(*S*))].[8g] IR ν_{max}/cm^{-1} (film) 3435, 3032, 2920, 1552, 1379, 1066; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.08(s, 1H), 4.47–4.62 (m, 2H), 5.42–5.44 (d, *J* = 8.0 Hz, 1H), 7.36–7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 71, 81.2, 125.9,, 128.9, 129, 138.1.

4.4.2. (*S*)-1-(2-Methoxyphenyl)-2-nitroethanol 7b

80% Yield, 90% ee, yellow oil; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85:15 *v*/*v*, 0.8 mL/min, 23 °C, UV 215 nm): $t_{R(minor)}$ = 14.37 min, $t_{R(major)}$ = 16.65 min; $[\alpha]_D^{25} = +35.5$ (*c* 0.40, CH_2Cl_2, 90% ee), [lit. $[\alpha]_D^{25} = +33.2$ (*c* 7.06, CH_2Cl_2, 85% ee(*S*))].[8g] IR ν_{max}/cm^{-1} (film) 3543, 3011, 2943, 2841, 1554, 1379, 1072; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.13–3.15 (d, *J* = 8.0 Hz, 1H), 3.88 (s, 3H), 4.54–4.67 (m, 2H), 5.61–5.65 (m, 1H), 6.90–6.92 (d, *J* = 8.0 Hz, 1H), 6.99–7.03 (t, *J* = 16.0 Hz, 1H), 7.31–7.35 (t, *J* = 16.0 Hz, 1H),7.43–7.45 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 67.8, 79.8, 110.5, 121.1, 125.9, 127.2, 129.8, 156.0.

4.4.3. (*S*)-1-(3-Methoxyphenyl)-2-nitroethanol 7c

80% Yield, 88% ee, colorless oil; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 90:10 *v*/*v*, 1 mL/min, 23 °C, UV 215 nm): $t_{R(minor)}$ = 21.64 min, $t_{R(major)}$ = 29.29 min; $[\alpha]_D^{25} = +30.80$ (*c* 0.44, CH_2Cl_2, 88% ee), [lit. $[\alpha]_D^{25} = -33.2$ (*c* 0.27, CH_2Cl_2, 95% ee(*R*))].[5d] IR ν_{max}/cm^{-1} (film) 3483, 3011, 2943, 2839, 1556, 1157, 1039; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.79 (s, 1H), 3.82–3.84 (d, *J* = 8.0 Hz, 3H), 4.49–4.63 (m, 2H), 5.46 (s, 1H), 6.88–6.97 (m, 2H), 7.25–7.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 70.9, 81.2, 111.5, 114.3, 118.0, 130.1, 139.8, 160.0.

4.4.4. (*S*)-1-(3-Methylphenyl)-2-nitroethanol 7d

85% Yield, 88% ee, colorless oil; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85:15 *v*/*v*, 0.8 mL/min, 23 °C, UV 254 nm): $t_{r(minor)}$ = 10.34 min, $t_{R(major)}$ = 11.7 min; $[\alpha]_D^{25} = +31.1$ (*c* 0.46, CH_2Cl_2, 88% ee), [lit. $[\alpha]_D^{25} = +31.8$ (*c* 5.82, CH_2Cl_2, 91% ee(*S*))].[8g] IR ν_{max}/cm^{-1} (film) 3531, 3109, 2972, 1633, 1556, 1340, 1089; ^{1}H NMR (400 MH_Z, $CDCl_3$) δ 2.37 (s, 3H), 2.74–2.75 (d, *J* = 4.0 Hz, 1H), 4.49–4.64

(m, 2H), 5.42–5.45 (t, J = 12.0 Hz, 1H), 7.16–7.31 (m, 4H); ^{13}C NMR (100 MH_Z, $CDCl_3$) 21.3, 71.0, 81.2, 123.0, 126.6, 128.9, 129.6, 138.1, 138.6.

4.4.5. (*S*)-1-(4-Methylphenyl)-2-nitroethanol 7e

65% Yield, 78% ee, colorless oil; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85:15 *v*/*v*, 0.8 mL/min, 23 °C, UV 215 nm): $t_{R(minor)}$ = 11.9 min, $t_{R(major)}$ = 14.46 min; $[\alpha]_D^{25} = +12.9$ (*c* 0.50, EtOH, 78% ee), [lit. $[\alpha]_D^{25} = +15.2$ (*c* 3.62, EtOH, 90% ee(*S*))].[8g] IR ν_{max}/cm^{-1} (film) 3537, 2922, 1614, 1554, 1379, 1078; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.84(s, 1H), 4.47–4.63 (m, 2H), 5.41–5.43 (d, J = 8.0 Hz, 1H), 7.20–7.22(d, J = 8.0 Hz, 2H), 7.27–7.29 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 21.1, 70.9, 81.2, 125.8, 129.6, 135.1, 138.9.

4.4.6. (*S*)-1-(2-Chlorophenyl)-2-nitroethanol 7f

80% Yield, 86% ee, colorless oil; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 98:2 *v*/*v*, 1 mL/min, 23 °C, UV 215 nm): $t_{R(minor)}$ = 27.84 min, $t_{R(major)}$ = 29.70 min; $[\alpha]_D^{25} = +50.1$ (*c* 0.40, CH_2Cl_2, 86% ee), [lit. $[\alpha]_D^{23} = -52.7$ (*c* 1.21, CH_2Cl_2, 91% ee(*R*)).[3b] IR ν_{max}/cm^{-1} (film) 3530, 2924, 1556, 1379, 1087; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.10 (s, 1H), 4.42–4.68 (m, 2H), 5.82–5.85 (d, J = 12.0 Hz, H), 7.28–7.39 (m, 3H), 7.65–7.66 (d, J = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 67.8, 79.3, 127.5, 127.6, 129.7, 129.9, 131.4, 135.5.

4.4.7. 1-(3-Chlorophenyl)-2-nitroethanol 7g

70% Yield, 78% ee, colorless oil; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85:15 *v*/*v*, 0.8 mL/min, 23 °C, UV 215 nm): $t_{R(minor)}$ = 12.9 min, $t_{R(major)}$ = 16.0 min; $[\alpha]_D^{25} = +16.3$ (*c* 0.34, $CHCl_3$, 78% ee). IRν_{max}/cm^{-1} (film) 3450, 3069, 2922, 1556, 1379, 1076; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.0–3.0 (s, 1H), 4.49–4.61 (m, 2H), 5.44–5.46 (d, J = 8.0 Hz, 1H), 7.27–7.43 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.2, 80.9, 124.0, 126.2, 129.1, 130.3, 135.0, 140.0.

4.4.8. (*S*)-1-(4-Chlorophenyl)-2-nitroethanol 7h

65% Yield, 68% ee, colorless oil; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85:15 *v*/*v*, 0.8 mL/min, 23 °C, UV 215 nm): $t_{R(minor)}$ = 11.5 min, $t_{R(major)}$ = 13.9 min; $[\alpha]_D^{25} = +27.6$ (*c* 0.42, 'CH_2Cl_2, 68% ee), [lit. $[\alpha]_D^{25} = +36.7$ (*c* 4.42, CH_2Cl_2, 91% ee(*S*))].[8g] IR ν_{max}/cm^{-1} (film) 3543, 2922, 1552, 1379, 1089; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.96 (s, 1H), 4.47–4.60 (m, 2H), 5.44–5.46 (d, J = 8.0 Hz, 1H), 7.34–7.43 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.3, 81.0, 127.4, 129.3, 134.9, 136.6.

4.4.9. 1-(2-Bromophenyl)-2-nitroethanol 7i

75% Yield, 70% ee, colorless oil; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 97:3 *v*/*v*, 1 mL/min, 23 °C, UV 215 nm): $t_{R(minor)}$ = 24.0 - min, $t_{R(major)}$ = 26.0 min; $[\alpha]_D^{25} = +23.6$ (*c* 0.72, $CHCl_3$, 70% ee). IR ν_{max}/cm^{-1} (film) 3520, 2922, 1554, 1377, 1084; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.66 (d, J = 8.0 Hz, 1H), 7.55–7.57 (d, J = 8.0 Hz, 1H), 7.38–7.45 (m, 1H), 7.21–7.25(m, 2H), 5.78–5.81 (m, 1H), 4.40–4.70 (m, 2H), 3.12–3.13 (d, J = 4.0 Hz, 1H). 3.10 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.8, 79.3, 121.4, 127.8, 128.2, 130.2, 133.0, 137.1.

4.4.10. 1-(3-Bromophenyl)-2-nitroethanol 7j

78% Yield, 64% ee, colorless oil; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 90:10 *v*/*v*, 1 mL/min, 23 °C, UV 215 nm): $t_{R(minor)}$ = 15.7 min, $t_{R(major)}$ = 20.6 min; $[\alpha]_D^{25} = +15.2$ (*c* 0.46, $CHCl_3$, 64% ee). IR ν_{max}/cm−1 (film) 3443, 3065, 2922, 1556, 1379, 1072; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.97 (s, 1H), 4.50–4.62 (m, 2H), 5.45 (s, 1H), 7.27–7.60 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.2, 80.9, 123.1, 124.5, 129.1, 130.6, 132.0, 140.2.

4.4.11. (*S*)-1-(4-Bromophenyl)-2-nitroethanol 7k

70% Yield, 86% ee, colorless oil; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85:15 *v*/*v*, 0.8 mL/min, 23 °C, UV 215 nm): $t_{R(minor)}$ = 13.8 min, $t_{R(major)}$ = 17.4 min; $[\alpha]_D^{23} = +66.5$ (*c* 0.50, $CHCl_3$, 86% ee), [lit. $[\alpha]_D^{23} = -68.6$ (*c* 1.40, $CHCl_3$, 89% ee(*R*))].[15] IR ν_{max}/cm^{-1} (film) 3431, 2926, 1552, 1381, 1072; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.54 (m, 2H), 7.24–7.29 (m, 2H), 5.41–5.44 (m, 1H), 4.45–4.60 (m, 2H), 2.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.3, 80.9, 122.9, 127.6, 132.1, 137.0.

4.4.12. (*S*)-1-(4-Fluorophenyl)-2-nitroethanol 7l

80% Yield, 82% ee, colorless oil; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 90:10 *v*/*v*, 0.8 mL/min, 23 °C, UV 215 nm): $t_{R(minor)}$ = 14.5 min, $t_{R(major)}$ = 16.9 min; $[\alpha]_D^{25} = +31.0$ (*c* 0.56, EtOH, 82% ee), [lit. $[\alpha]_D^{25} = +34.0$ (*c* 6.74, CH_2Cl_2, 91% ee(*S*))].[8g] IR ν_{max}/cm^{-1} (film) 3431, 2924, 1556, 1379, 1224; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.40 (m, 2H), 7.06–7.15 (m, 2H), 5.42–5.45 (m, 1H), 4.46–4.60 (m, 2H), 3.08 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.3, 81.1, 116.1, 127.8, 161.6, 164.1.

4.4.13. (S)-1-Naphthyl-2-nitroethanol 7m

75% Yield, 72% ee, yellow solid; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85:15 *v*/*v*, 1 mL/min, 23 °C, UV 215 nm): $t_{R(minor)}$ = 11.5 min, $t_{R(major)}$ = 17.0 min; $[\alpha]_D^{21} = +13.8$ (*c* 0.42, CH_2Cl_2, 72% ee), [lit. $[\alpha]_D^{25} = +17.7$ (*c* 2.41, CH_2Cl_2, 93% ee (*S*))].[15] IR ν_{max}/cm^{-1} (film) 3404, 3057, 2918, 1554, 1379, 1097; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.85–2.86 (d, J = 4.0 Hz, 1H), 4.68–4.73 (m, 2H), 6.28–6.30(m, 1H), 7.51–7.62 (m, 3H), 7.77–7.79 (d, J = 8.0 Hz, 1H), 7.86–7.88 (d, J = 8.0 Hz, 1H), 7.91–7.93 (d, J = 8.0 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.3, 80.8, 121.8, 123.8, 125.5, 126.1, 127.0, 129.3, 129.4, 129.5, 133.5, 133.7.

4.4.14. (*S*)-1-(2-Naphthyl)-2-nitroethanol 7n

70% Yield, 82% ee, yellow solid; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85:15 *v*/*v*, 1.0 mL/min, 23 °C, UV 215 nm): $t_{R(minor)}$ = 25.1 min, $t_{R(major)}$ = 35.1 min; $[\alpha]_D^{25} = +30.0$ (*c* 0.46, CH_2Cl_2, 82% ee), [lit. $[\alpha]_D^{25} = +31.0$ (*c* 3.08, CH_2Cl_2, 86% ee(*S*))].[8g] IR ν_{max}/cm^{-1} (film) 3460, 2926, 1552, 1377, 1080; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.04–3.05 (d, J = 4.0, 1H), 4.56–4.70 (m, 2H), 5.59–5.62 (d, J = 12.0 Hz, 1H), 7.44–7.54 (m, 3H), 7.84–7.88 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.1, 81.9, 123.2, 125.3, 126.6, 126.7, 127.8, 128.0, 129.0, 133.1, 133.4, 135.4.

4.4.15. (*S*)-1-Furfuryl-2-nitroethanol 7o

80% Yield, 88% ee, white solid; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 90:10 *v*/*v*, 1.0 mL/min, 23 °C, UV 215 nm): $t_{R(minor)}$ = 22.8 min, $t_{R(major)}$ = 27.2 min; $[\alpha]_D^{25} = +33.5$ (*c* 0.42, CH_2Cl_2, 84% ee), [lit. $[\alpha]_D^{25} = -37.1$ (*c* 0.24, CH_2Cl_2, 98% ee(*R*))].[15] IR ν_{max}/cm^{-1} (film) 3447, 3126, 2926, 1556, 1381, 1068; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76–2.78 (d, J = 8.0 Hz, 1H), 4.64–4.82 (m, 2H), 5.46–5.51 (m, 1H), 6.38–6.41 (m, 2H), 7.42–7.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 64.9, 78.4, 108.2, 110.7, 143.2, 150.7.

4.4.16. (*S*)-1-(2-Nitrophenyl)-2-nitroethanol 7p

83% Yield, 84% ee; greenish solid; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85:15 *v*/*v*, 0.8 mL/min, 23 °C, UV 215 nm): $t_{R(minor)}$ = 11.8 min, $t_{R(major)}$ = 12.7 min; $[\alpha]_D^{25} = -210.9$ (*c* 0.64, CH_2Cl_2, 90% ee), [lit. $[\alpha]_D^{25} = -230.9$ (*c* 1.81, CH_2Cl_2, 92% ee)].[8g] IR ν_{max}/cm^{-1} (film) 3530, 1610, 1556, 1346, 1097; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.28 (s, 1H), 4.52–4.87 (m, 2H), 6.02–6.05 (d, J = 12.0 Hz, 1H), 7.52–7.56 (t, J = 16.0, 1H), 7.72–7.76 (t, J = 16.0 Hz, 1H), 7.93–7.95 (d, J = 8.0 Hz, 1H), 8.05–8.07 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 66.8, 80.0, 125.0, 128.6, 129.6, 134.0, 134.3, 147.1.

4.4.17. (*S*)-1-(3-Nitrophenyl)-2-nitroethanol 7q

85% Yield, 78% ee, yellow solid; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85:15 *v*/*v*, 0.8 mL/min, 23 °C, UV 215 nm): $t_{R(\text{minor})}$ = 18.5 min, $t_{R(\text{major})}$ = 20.5 min; $[\alpha]_D^{25} = +28.1$ (*c* 0.46, CH_2Cl_2, 78% ee), [lit. $[\alpha]_D^{20} = +24.0$ (*c* 1.65, CH_2Cl_2, 67% ee(*S*))].[8h] IR ν_{max}/cm^{-1} (film) 3545, 3092, 2924, 1556, 1527, 1354, 1072; ^1H NMR (400 MHz, $CDCl_3$) δ 3.13 (s, 1H), 4.56–4.66 (m, 2H), 5.60–5.61 (d, *J* = 4.0 Hz, 1H), 7.59–7.63 (m, 1H), 7.76–7.78 (d, *J* = 8.0 Hz, 1H), 8.22–8.24 (d, *J* = 8.0 Hz, 1H), 8.33 (s, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) 69.8, 80.6, 121.1, 123.8, 130.1, 132.0, 140.2, 148.5.

4.4.18. (*S*)-1-(4-Nitrophenyl)-2-nitroethanol 7r

90% Yield, 74% ee, colorless oil; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85:15 *v*/*v*, 0.8 mL/min, 23 °C, UV 215 nm): $t_{R(\text{minor})}$ = 19.5 min, $t_{R(\text{major})}$ = 23.7 min; $[\alpha]_D^{25} = +26.1$ (*c* 0.60, CH_2Cl_2, 74% ee), [lit. $[\alpha]_D^{25} = +29.4$ (*c* 2.36, CH_2Cl_2, 85% ee(*S*))].[8g] IR ν_{max}/cm^{-1} (film) 3543, 1556, 1520, 1381, 1082; ^1H NMR (400 MHz, $CDCl_3$) δ 3.43 (s, 1H), 4.56–4.64 (m, 2H), 5.60 (s, 1H), 7.60–7.62 (d, *J* = 8.0 Hz, 2H), 8.21–8.23 (d, *J* = 8.0 Hz, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.9, 80.6, 124.1, 127.0, 145.2, 148.0.

4.4.19. 1-(3-Hydroxyphenyl)-2-nitroethanol 7s

75% Yield, 80% ee, white solid; HPLC (Chiralcel AD-H, *n*-hexane/*i*-PrOH, 85:15 *v*/*v*, 0.8 mL/min, 23 °C, UV 215 nm): $t_{R(\text{minor})}$ = 13.5 min, $t_{R(\text{major})}$ = 15.7 min; $[\alpha]_D^{25} = +8.1$ (*c* 0.55, EtOH, 80% ee). IR ν_{max}/cm^{-1} (film) 3543, 1556, 1520, 1381, 1082; 1H NMR (400 MHz, $CDCl_3$) δ 3.34 (s, 1H), 4.56–4.57 (m, 2H), 5.32–5.36 (m, 1H), 6.76–6.78 (m, 1H), 6.87–6.89 (m, 2H), 7.18–7.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 74.5, 85.5, 116.5, 119.2, 120.9, 133.6, 144.8, 161.1.

4.4.20. (*S*)-2-Nitro-1-cyclohexylethanol 7t

90% Yield, 88% ee, colorless oil; HPLC (Chiralcel AD-H, *n*-hexane/*i*-PrOH, 97:3 *v*/*v*, 0.8 mL/min, 23 °C, UV 215 nm): $t_{R(\text{minor})}$ = 11.9 min, $t_{R(\text{major})}$ = 14.1 min; $[\alpha]_D^{25} = +15.5$ (*c* 0.6, CH_2Cl_2, 84% ee), [lit. $[\alpha]_D^{25} = +16.7$ (*c* 4.13, CH_2Cl_2, 91% ee(*S*))].[8g] IR ν_{max}/cm^{-1} (film) 3431, 2928, 2854, 1554, 1385, 1097; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23–1.30 (m, 5H), 1.42–1.51 (m, 1H), 1.65–1.84 (m, 5H), 2.52 (s, 1H), 4.08 (s, 1H), 4.38–4.49 (m, 2H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.7, 25.8, 26.0, 27.9, 28.8, 41.4, 72.8, 79.3.

4.4.21. (*S*)-3-Methyl-1-nitrobutan-2-ol 7u

90% Yield, 86% ee, colorless oil; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 97:3 *v*/*v*, 0.6 mL/min, 23 °C, UV 220 nm): $t_{R(\text{minor})}$ = 27.6 min, $t_{R(\text{major})}$ = 30.0 min; $[\alpha]_D^{25} = +19.5$ (*c* 0.5, $CHCl_3$, 84% ee), [lit. $[\alpha]_D^{25} = +20.4$ (*c* 1.0, $CHCl_3$, 91% ee (*S*))].[8g] IR ν_{max}/cm^{-1} (film) 3431, 2968, 1552, 1385, 1070; ^1H NMR (400 MHz, $CDCl_3$) δ 0,97–1.00 (m, 6H), 1.77–1.81 (m, 1H), 2.57 (s, 1H), 4.10 (s, 1H), 4.37–4.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 18.4, 31.7, 73.3, 79.2.

4.4.22. (*S*)-4-Methyl-1-nitropentan-2-ol 7v

90% Yield, 88% ee, colorless oil; HPLC (Chiralcel OJ-H, *n*-hexane/*i*-PrOH, 85:15 *v*/*v*, 0.8 mL/min, 23 °C, UV 215 nm): $t_{R(\text{minor})}$ = 11.9 - min, $t_{R(\text{major})}$ = 14.1 min; $[\alpha]_D^{25} = -2.17$ (*c* 0.42, CH_2Cl_2, 88% ee), [lit. $[\alpha]_D^{25} = -2.2$ (*c* 1.95, CH_2Cl_2, 87% ee(*S*))].[3b,4] IR ν_{max}/cm^{-1} (film) 3414, 2961, 1556, 1386, 1089; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90–0.98 (m, 6H), 1.02–1.27 (m, 1H), 1.48–1.55 (m, 1H‘), 1.81–1.86 (m, 1H), 2.50 (s, 1H), 4.33–4.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 23.1, 24.3, 42.4, 66.9, 80.9.

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