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Asymmetric Henry reaction catalyzed by a chiral Cu(II) complex: a facile enantioselective synthesis of (*S*)-2-nitro-1-arylethanols

Basi V. Subba Reddy *, Sankham Madhusudana Reddy, Swain Manisha, Chinnala Madan

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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ABSTRACT

A catalytic asymmetric Henry reaction has been developed using a novel chiral Cu(II) complex derived from (*R*)-2-(diphenylmethanol)-l-(2-pyridylmethyl)pyrrolidine and copper(II) acetate in ethanol under mild conditions. The corresponding chiral 2-nitro-1-arylethanol derivatives were obtained in high yields with moderate to good enantiomeric excess (up to 86% ee). The results indicate that the coordination of a metal atom to the nitrogen of the pyridine ring is essential in determining the stereochemistry of the process.

1. Introduction

β-Adrenergic drugs have historically been made as racemates; however, there is an increasing demand for a single enantiomer because the biological activity resides mainly in the (*R*)-enantiomer of the drug.[1] Thus, the preparation of enantiomerically pure β-adrenergic blockers has received a great deal of attention. Generally, the synthesis of β-adrenergic blockers involves chemical resolutions or rather lengthy chemical syntheses from chiral precursors (Fig. 1).[2–5]

The 2-nitro-1-arylalkanols are key intermediates for the synthesis of β-adrenergic drugs.[6] Generally, 2-nitroalkanols are prepared via the Henry reaction.[7,8] However, asymmetric version of Henry reaction promoted by chiral catalysts had not appeared until the last decade.

The first asymmetric Henry reaction was reported by Shibasaki and co-workers[9] using a series of heterobimetallic catalysts.[10] Subsequently, several elegant approaches have been developed for the asymmetric Henry reaction using organocatalysts.[11–13] However, some of these catalytic systems show some limitations, such as moisture or air sensitivity, high catalyst loading, low enantioselectivity, or the difficult preparation of the catalyst.[14] Therefore, the development of simple and readily available chiral copper(II) complexes would certainly expand the scope of the asymmetric Henry reaction.

2. Results and discussion

Chiral ligand **3** was prepared from (*R*)-diphenyl prolinol and 2-bromomethylpyridine hydrobromide using K_2CO_3 and KI in ethanol (Scheme 1).[15a]

Similarly, chiral ligand **5** was prepared from (*R*)-diphenyl prolinol and 2,6-bis(bromomethyl)pyridine using K_2CO_3 and KI in ethanol (Scheme 2).[15b]

Herein, we report a catalytic enantioselective Henry reaction of various aromatic and aliphatic aldehydes with nitromethane using a chiral copper(II) complex prepared from (*R*)-2-(diphenylmethanol)-l-(2-pyridylmethyl)pyrrolidine **3** and $Cu(OAc)_2$. Initially, the catalyst was prepared using 5 mol % of ligand **3** and 4.9 mol % of $Cu(OAc)_2$ in ethanol at room temperature. The chiral Cu(II) complex prepared was used for the asymmetric Henry reaction. As a model reaction, *p*-chlorobenzaldehyde was treated with nitromethane in the presence of 5 mol % of chiral Cu(II) complex in ethanol. The reaction proceeded smoothly at 25 °C under mild conditions and the corresponding (*S*)-1-(4-chlorophenyl)-2-nitroethanol was obtained in 88% yield with 86% ee (Table 4, entry **7**c, Scheme 3).

To determine the effect of the catalyst, the reaction was performed with different copper salts, such as $Cu(OAc)_2{\cdot}H_2O$, $Cu(OAc)_2$, and $Cu(OTf)_2$. Of these, anhydrous $Cu(OAc)_2$ was found to be superior in terms of yield and enantiomeric excess and the results are presented in Table 1.

The scope of the reaction was studied with various copper(II) salts both in the presence and absence of a base. Hydrated copper(II) acetate was found to be less effective than the anhydrous one (Table 1, entry a).

Furthermore, the combination of copper(II) triflate and triethyl amine was also not effective (Table 1, entry b). It is important to mention that enantiomeric excess decreased dramatically by the addition of triethylamine to anhydrous $Cu(OAc)_2$ (Table 1, entry e). However, the combination of ligand **5** with anhydrous $Cu(OAc)_2$ also gave the product in good yield but the ee (Table 1, entry f) was very low. Therefore, the use of ligand **3** and anhydrous $Cu(OAc)_2$ was found to give the best results (Table 1, entry d).

* Corresponding author. Fax: +91 40 27160512.
E-mail address: basireddy@iict.res.in (Basi V. Subba Reddy).

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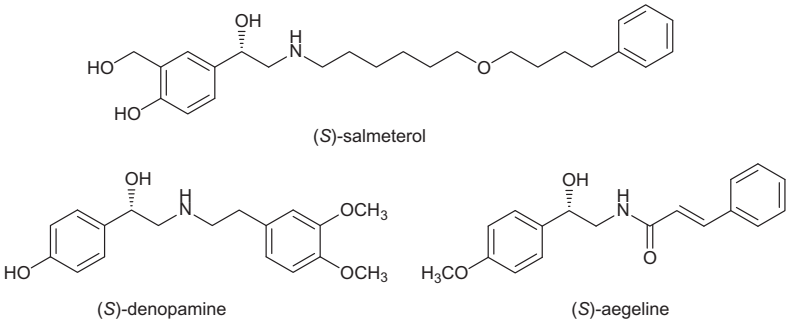
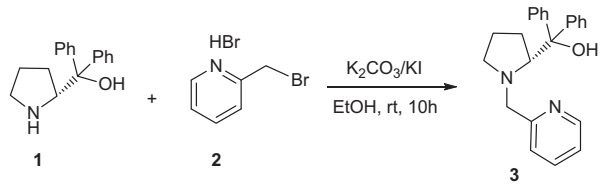
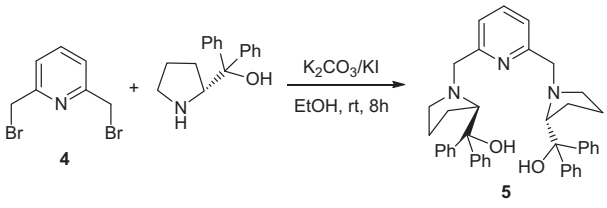


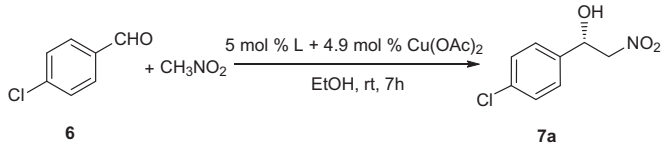
Figure 1. Examples of optically active β-adrenergic blockers.



Scheme 1. Synthesis of (*R*)-2-(diphenylmethanol)-l-(2-pyridylmethyl)pyrrolidine **3**.



Scheme 2. Synthesis of ((2*R*,2′*R*)-1,1′-(2,6-pyridinyldimethyl))bis[2-(diphenylmethanol)pyrrolidine] **5**.



Scheme 3. Synthesis of (*S*)-1-(4-chlorophenyl)-2-nitroethanol.

Table 1
Effect of various copper(II) salts in the synthesis of **7a** using ligand **3**[a]

Entry	L	Solvent	Time (h)	Yield (%)	ee (%)
a	**3**	$Cu(OAc)_2 \cdot H_2O$	8.0	80	78
b	**3**	$Cu(OTf)_2$	40 (Et_3N)/0 °C	62	56[b]
c	**3**	$Cu(OTf)_2$	24	0	0
d	**3**	$Cu(OAc)_2$	7.0	88	86
e	**3**	$Cu(OAc)_2$	36 (Et_3N)/0 °C	55	11[b]
f	**5**	$Cu(OAc)_2$	8.0	75	3

[a] The reactions were carried out at 0.5 mmol scale using 0.05 mmol L, 0.049 mmol % Cu(II) at rt.
[b] Effect of base in reaction rate and ee value.

Next we have examined the effect of various solvents on the nitroaldol reaction of 4-chlorobenzaldehyde with nitromethane using a 5 mol % chiral copper(II) complex. The results are summarized in Table 2. As can be seen in Table 2, protic solvents (alcohols) are superior to aprotic solvents. The enantioselectivity increases in the following order CH_2Cl_2 < THF < toluene < MeOH < EtOH. Surprisingly, the ee was low in acetonitrile (Table 2, entry d).

Table 2
Effect of solvent in the synthesis of **7a** using chiral catalyst **3**

Entry	Solvent	Time (h)	Yield[a] (%)	ee (%)
a	MeOH	7	86	81
b	EtOH	7	88	86
c	CH_2Cl_2	12	60	60
d	MeCN	9	70	40
e	Toluene	15	55	70
f	THF	11	80	66

[a] Yield refers to pure products after chromatography.

To investigate the effect of the quantity of the catalyst on enantioselectivity, we carried out the reactions by varying the amount of the catalyst (Table 3). Although, the reaction proceeds with low catalyst loading (1 mol %, Table 3, entry a), the reaction requires a long reaction time (14 h). There was no considerable difference in reaction rates or ee using either 5 mol % or 10 mol % of the catalyst (Table 3, entries b and c). However, the use of 20 mol % catalyst gave the product with a lower ee (Table 3, entry d).

Table 3
Effect of quantity of the chiral catalyst **3** in the preparation of **7a**

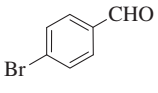
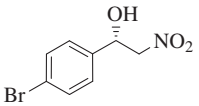
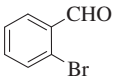
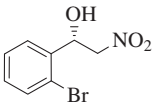
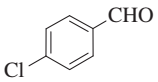
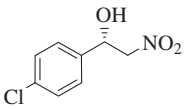
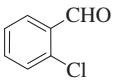
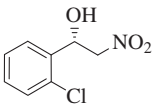
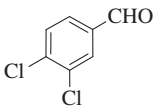
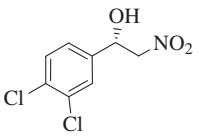
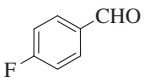
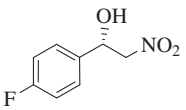
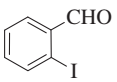
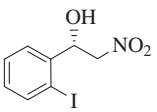
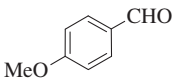
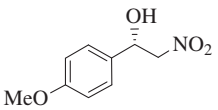
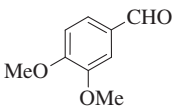
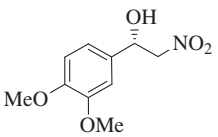
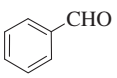
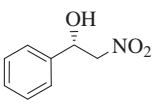
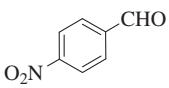
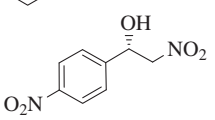
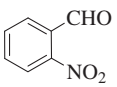
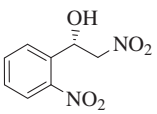
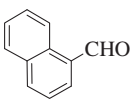
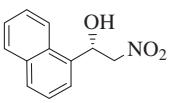
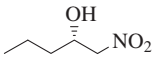
Entry	Mol (%)	Time (h)	Yield[a] (%)	ee (%)
a	1	14	60	70
b	5	7	88	86
c	10	7	88	85
d	20	7	87	78

[a] Yield refers to pure products after chromatography.

In order to examine the scope of this transformation, the reactions were carried using various substrates as shown in Table 4. A wide range of aryl aldehydes participated well in this reaction affording the corresponding 2-nitro-1-alkanols in high yields and with good enantiomeric excess in the range of 50–86%. It is noteworthy that this method works well even with aliphatic aldehydes. It should be noted that *n*-butyraldehyde gave the nitroalkanol in 75% yield with 77% ee under similar conditions. Aryl aldehydes containing either an electron-donating or electron-withdrawing substituent on the aromatic ring gave the nitroalkanols in high yields (Table 4). For example, 3,4-dimethoxybenzaldehyde gave the corresponding nitroalcohol in 86% yield with 82% ee (Table 4, entry i). Notably, a sterically hindered 1-naphthaldehyde also gave the (*S*)-2-nitro-arylethanol in 78% yield with 81% ee (Table 4, entry m).

The absolute configuration of the newly generated stereogenic center of the nitroaldol products was assigned by comparison with literature compounds.[16] Additional analyses were made by converting the (*S*)-1-(4-chlorophenyl)-2-nitroethanol **7c** into the known (*S*)-2-amino-1-(4-chlorophenyl)ethanol.[17] It is likely that the absolute configuration of the remaining examples is the same.

Table 4
Catalytic asymmetric Henry reaction catalyzed by chiral Cu(II) complex (**3**)

Entry	Aldehyde (**6**)	Product (**7**)[a]	Time (h)	Yield[b] (%)	ee[c] (%)	Configuration[d]
a			10	81	82	(*S*)
b			8	82	73	(*S*)
c			7	88	86	(*S*)
d			6	82	76	(*S*)
e			10	84	74	(*S*)
f			6	85	75	(*S*)
g			8	75	68	(*S*)
h			12	76	82	(*S*)
i			14	86	82	(*S*)
j			8	79	50	(*S*)
k			6	91	53	(*S*)
l			6	85	81	(*S*)
m			8	78	81	(*S*)
n			7	75	77	(*S*)

[a] All products were characterized by ^{1}H NMR, IR and mass spectroscopy.
[b] Yield refers to pure products after chromatography.
[c] The ee value of the product was determined by chiral HPLC analysis.
[d] The absolute configuration was assigned by the sign of the rotation.

The results can be rationalized by the transition state model as shown in Figure 2. The reaction may involve Cu(II)-mediated dual activation of both the nitronate and aldehyde. In the transition state, the nucleophilic carbon of the nitronate ion formed in situ by the deprotonation of nitromethane with an acetate ion attacks the aldehyde from the *Si* face to afford the (*S*)-isomer as a major product. *Re* face attack is not favorable due to severe non-bonding interactions between the aromatic group or aliphatic chain of the corresponding aldehyde with the ligand **3**, ((*R*)-2-(diphenylmethanol)-l-(2-pyridylmethyl)pyrrolidine (Fig. 2).

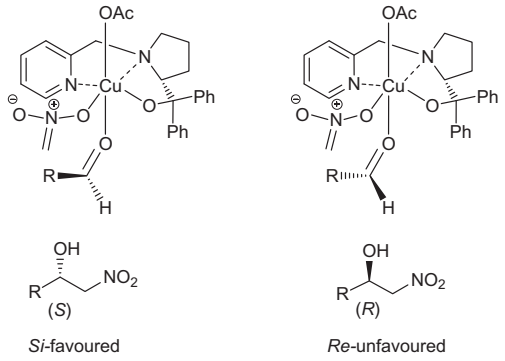


Figure 2. A plausible stereochemical model.

The (*S*)-configuration of the nitroalkanols was further confirmed by comparing their specific rotations with authentic samples.[16]

3. Conclusion

In conclusion, we have demonstrated an efficient catalytic asymmetric Henry reaction of aromatic and aliphatic aldehydes with nitromethane using a novel chiral Cu(II) complex to produce 2-nitro-1-alkanol derivatives in high yields and with moderate to good enantioselectivity. This method provides an easy access for the synthesis of chiral 2-nitroalkanols from both aromatic and aliphatic aldehydes which may find wide application in medicinal chemistry.

4. Experimental

4.1. General

The spectroscopic data of ^{1}H and ^{13}C NMR were recorded in $CDCl_3$ solvent on a Bruker AV-300 MHz spectrometer and chemical shifts are reported in ppm. Mass spectra were recorded on a VG micromass-7070H (70 eV). CHN analysis was performed on a Vario EL analyzer. The optical rotations were recorded on a Perkin–Elmer (model 343) digital polarimeter. HPLC analysis was performed on a Schimadzu liquid chromatography LC-6A, equipped with a SCE-6A, system controller, SPD-6A, fixed wavelength UV monitor as detector and chromatopac C-R4A data processor as integrator. The column was 4.6 × 250 mm, Chiralcel OD-H, AD-H and OJ-H columns. All the starting materials were prepared according to literature procedures. All products were purified by column chromatography on silica gel (Merck 60–120 mesh), using a gradient mixture of petroleum ether/EtOAc as eluent.

4.2. Typical procedure for the preparation of the ligand 3

A solution of (*R*)-1,1-diphenyl-2-pyrrolidinemethanol (0.25 g, 1 mmol) 2-bromomethyl pyridine hydrobromide (0.25 g, 1 mmol), K_2CO_3 (0.27 g, 2 mmol) and KI (10 mg) in ethanol (15 mL) was stirred at room temperature for 10 h. The solution was filtered and the solvent was removed in vacuo. Then the mixture was diluted with water (50 mL) and the aqueous solution was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was concentrated and the crude product was purified by column chromatography (*n*-hexane/ethyl acetate, 1:1) to afford the pure (*R*)-2-(diphenylmethanol)-l-(2-pyridylmethyl) pyrrolidine **3** as a colorless solid in 76% yield (0.26 g).[18]

4.3. Spectroscopic data for the (*R*)-2-(diphenylmethanol)-l-(2-pyridylmethyl)pyrrolidine

Solid, mp 114–116 °C, $[\alpha]_D^{29} = -64.0$ (*c* 0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.42–8.39 (m, 1H), 7.70–7.53 (m, 5H), 7.31–7.01 (m, 8H), 4.98 (s, 1H), 4.06 (q, *J* = 4.6 Hz, 1H), 3.33 (s, 2H), 3.00–2.95 (m, 1H), 2.60–2.48 (m, 1H), 1.95–1.60 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6, 148.5, 147.7, 146.4, 136.2, 128.0, 127.9, 126.3, 126.2, 125.5, 122.4, 121.7, 78.0, 70.8, 62.1, 55.6, 29.5, 24.3; MS (MSD): *m*/*z* 345 [M^{+1}].

4.4. Typical procedure for the preparation of the ligand 5

A solution of (*R*)-1,1-diphenyl-2-pyrrolidinemethanol (0.50 g, 2 mmol) 2,6-bis(bromomethyl)pyridine (0.25 g, 1 mmol), K_2CO_3 (0.54 g, 4 mmol) and KI (20 mg) in ethanol (30 mL) was stirred at room temperature for 8 h. The solution was filtered and the solvent was removed in vacuo. Then the mixture was diluted with water (75 mL) and the aqueous solution was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was concentrated and the crude product was purified by column chromatography (*n*-hexane/ethyl acetate, 1:1) to afford pure ((2*R*,2′*R*)-1,1′-(2,6-pyridinyldimethyl))bis[2-(diphenylmethanol)pyrrolidine] **5** as a colorless solid in 78% yield.

4.5. Spectroscopic data for the ((2*R*,2′*R*)-1,1′-(2,6-pyridinyldimethyl))bis[2-(diphenylmethanol) pyrrolidine]

Solid, mp 208–210 °C $[\alpha]_D^{20} = -39.6$ (*c* 0.3, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.36 Hz, 4H), 7.54–7.47 (m, 4H), 7.43–7.35 (m, 1H), 7.28–6.93 (m, 12H), 6.79 (d, *J* = 7.5 Hz, 2H), 4.10–3.96 (m, 2H), 3.25 (s, 4H), 2.91–2.80 (m, 2H), 2.41 (q, *J* = 8.3 Hz, 2H), 1.96–1.44 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.6, 156.2, 155.3, 147.6, 146.2, 138.0, 137.2, 128.0, 127.9, 126.75, 126.3, 126.2, 126.1, 125.74, 125.54, 122.0, 121.6, 120.7, 77.9, 70.8, 61.7, 55.64, 46.6, 29.5, 24.3; IR (KBr): ν 3343, 3085, 3028, 2940, 2870, 2830, 2796, 1585, 1490, 1458, 1448, 1377, 1299, 1170, 1111; MS (MSD): *m*/*z* 610 [M^{+1}].

4.6. General procedure for the enantioselective Henry reaction

To an oven dried 25 mL two necked round-bottomed flask, a solution of ligand **3** (17.2 mg, 0.05 mmol) and $Cu(OAc)_2$. (8.9 mg, 0.049 mmol) in EtOH (1 mL) was stirred for 2 h at 25 °C. Then the aldehyde (1 mmol) and nitromethane (5 mmol) were added and the resulting mixture was stirred at 25 °C for the appropriate time (Table 4). After completion as monitored by TLC, the solvent was removed and the resulting residue was purified by column chromatography on silica gel (Merck, 60–120 mesh, (ethyl acetate/hexane, 1:9) to afford the pure 2-nitroalcohol.

4.6.1. (*S*)-1-(4-Bromophenyl)-2-nitroethanol 7a

81% Yield, 82% ee; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85:15 v/v, 0.8 mL/min, 23 °C, UV = 215 nm): t_r(minor) = 13.4 min,

t_r(major) = 16.8 min; $[\alpha]_D^{23} = +63.2$ (*c* 0.6, $CHCl_3$, 82% ee). ^1H NMR (300 MHz, $CDCl_3$): δ 7.50–7.54 (m, 2H), 7.25–7.29 (m, 2H), 5.41–5.43 (m, 1H), 4.45–4.60 (m, 2H), 3.45 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.0, 132.3, 127.6, 122.9, 80.9, 70.3; MS (EI): *m*/*z* 245 [M^+], 247 [M^{+2}].

4.6.2. (*S*)-1-(2-Bromophenyl)-2-nitroethanol 7b

82% Yield, 73% ee; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 97:3 v/v, 1 mL/min, 23 °C, UV = 215 nm): t_r(minor) = 23.8 min, t_r(major) = 25.9 min; $[\alpha]_D^{25} = -27.3$ (*c* 1.12, CH_2Cl_2, 73% ee). ^1H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, *J* = 7.7 Hz, 1H), 7.54(d, *J* = 7.9 Hz, 1H), 7.38(t, *J* = 7.7 Hz, 1H,), 7.27–7.15 (m, 1H), 5.76 (d, *J* = 9.6 Hz, 1H), 4.66 (dd, *J* = 2.26, 13.6 Hz, 1H), 4.43–4.29 (m, 1H), 3.29–3.17 (br s, 1H); ^{13}C NMR(75 MHz, $CDCl_3$): δ 137.0, 133.0, 130.2, 128.2, 127.8, 121.4, 79.3, 70.0; MS (EI): *m*/*z* 245 [M^+], 247 [M^{+2}].

4.6.3. (*S*)-1-(4-Chlorophenyl)-2-nitroethanol 7c

88% Yield, 86% ee; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85:15 v/v 1 mL/min, 23 °C, UV = 215 nm): t_r(minor) = 9.4 min, t_r(major) = 11.4 min; $[\alpha]_D^{25} = +34.8$ (*c* 1.02, CH_2Cl_2, 86% ee). ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–7.30 (m, 4H), 5.41 (dd, *J* = 8.3, 3.3 Hz, 1H), 4.58–4.34 (m, 2H), 3.21–2.96 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.5, 134.6, 129.1, 127.3, 80.8, 70.1; MS (EI): *m*/*z* 201 [M^+].

4.6.4. (*S*)-1-(2-Chlorophenyl)-2-nitroethanol 7d

82% Yield, 76% ee; HPLC (Chiralcel OJ-H, *n*-hexane/*i*-PrOH, 90:10 v/v, 1 mL/min, 23 °C, UV = 214 nm): t_r(minor) = 14.3 min, t_r(major) = 15.8 min; $[\alpha]_D^{25} = +44.2$ (*c* 0.46, CH_2Cl_2, 76% ee). ^1H NMR (300 MHz, $CDCl_3$): δ 7.63–7.26 (m, 4H), 5.83–5.80 (m, 1H), 4.65 (dd, *J* = 13.7, 2.5 Hz, 1H), 4.42 (dd, *J* = 13.7, 9.8 Hz, 1H), 3.02 (d, *J* = 4.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.5, 131.5, 129.9, 129.7, 127.6, 127.5, 79.3, 67.8; MS (EI): *m*/*z* 201 [M^+].

4.6.5. (*S*)-1-(3,4-Dichlorophenyl)-2-nitroethanol 7e

84% Yield, 74% ee; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85:15 v/v, 0.8 mL/min, 23 °C, UV = 215 nm): t_r(minor) = 12.6 min, t_r(major) = 16.1 min; $[\alpha]_D^{27} = +26.0$ (*c* 1.43, CH_2Cl_2, 74% ee). ^1H NMR (300 MHz, $CDCl_3$): δ 7.38 (s, 1H), 7.37 (d, *J* = 9.0 Hz, 1H), 7.14 (d, *J* = 9.0 Hz, 1H), 5.24 (dd, *J* = 9.3, 3.3 Hz, 1H), 4.58 (dd, *J* = 9.3, 13.2 Hz, 1H), 4.37 (dd, *J* = 3.3, 13.2 Hz, 1H), 3.59 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.0, 134.9, 132.2, 131.2, 130.8, 128.4, 83.8, 71.8; MS (ESI): *m*/*z* 236 [M^{+1}].

4.6.6. (*S*)-1-(4-Fluorophenyl)-2-nitroethanol 7f

85% Yield, 75% ee; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 90:10 v/v, 0.8 mL/min, 23 °C, UV = 215 nm): t_r(minor) = 15.3 min, t_r(major) = 17.8 min; $[\alpha]_D^{25} = +28.0$ (*c* 0.62, CH_2Cl_2, 75% ee). ^1H NMR (300 MHz, $CDCl_3$): δ 7.36–7.40 (m, 2H), 7.06–7.14 (m, 2H), 5.40–5.43 (m, 1H), 4.45–4.60 (m, 2H), 3.12 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.0, 161.5, 127.7, 116.0, 81.1, 70.3; MS (EI): *m*/*z* 185 [M^+].

4.6.7. (*S*)-1-(2-Iodophenyl)-2-nitroethanol 7g

75% Yield, 68% ee; HPLC (Chiralcel AD-H, *n*-hexane/*i*-PrOH, 95:5 v/v, 0.5 mL/min, 23 °C, UV = 214 nm): t_r(major) = 35.1 min, t_r(minor) = 38.0 min; $[\alpha]_D^{25} = +23.2$ (*c* 1.02, CH_2Cl_2, 68% ee). ^1H NMR (300 MHz, $CDCl_3$): δ 7.84 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.62 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.43 (td, *J* = 7.8, 1.5 Hz, 1H), 7.07 (td, *J* = 7.8, 1.2 Hz, 1H), 5.66 (dd, *J* = 9.9, 2.4 Hz, 1H), 4.65 (dd, *J* = 13.5, 2.4 Hz, 1H), 4.40(dd, *J* = 13.5, 9.9 Hz, 1H), 3.01 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.8, 139.6, 130.4, 129.0, 127.6, 96.6, 79.4, 74.3; MS (EI): *m*/*z* 293 [M^+].

4.6.8. (*S*)-1-(4-Methoxyphenyl)-2-nitroethanol 7h

76% Yield, 82% ee; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85:15 v/v, 0.8 mL/min, 23 °C, UV = 215 nm): t_r(minor) = 16.6 min, t_r(major) = 20.6 min; $[\alpha]_D^{25} = +33.8$ (*c* 1.02, CH_2Cl_2, 82% ee). ^1H NMR (300 MHz, $CDCl_3$): δ 7.32(d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 5.41 (dd, *J* = 9.3, 3.0 Hz,1H), 4.60–4.47 (m, 2H), 3.81 (s, 3H), 2.80 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.8, 130.2, 127.2, 114.3, 81.2, 70.6, 55.3; MS (EI): *m*/*z* 197 [M^+].

4.6.9. (*S*)-1-(3,4-Dimethoxyphenyl)-2-nitroethanol 7i

86% Yield, 82% ee; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85:15 v/v, 0.8 mL/min, 23 °C, UV = 215 nm): t_r(minor) = 24.2 min, t_r(major) = 31.3 min; $[\alpha]_D^{25} = +28.1$ (*c* = 1.2, CH_2Cl_2, 82% ee). ^1H NMR (300 MHz, $CDCl_3$): δ 6.91–6.83 (m, 3H), 5.38 (dt, *J* = 9.3, 2.7 Hz, 1H), 4.59–4.48 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.3, 130.7, 118.3, 111.3, 108.8, 81.3, 78.8, 55.9; MS (EI): *m*/*z* 227 [M^+].

4.6.10. (*S*)-1-Phenyl-2-nitro ethanol 7j

79% Yield, 50% ee; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85:15 v/v, 0.8 mL/min, 23 °C, UV = 215 nm): t_r(minor) = 9.6 min, t_r(major) = 11.0 min; $[\alpha]_D^{25} = +19.3$ (*c* 0.48, CH_2Cl_2, 50% ee). ^1H NMR (300 MHz, $CDCl_3$): δ 7.50–7.38 (m, 5H), 5.46 (dd, *J* = 9.3, 3.6 Hz, 1H), 4.62–4.46 (m, 2H), 2.78 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.1, 129.0, 128.9, 125.9, 81.2, 71.0; MS (EI): *m*/*z* 167 [M^+].

4.6.11. (*S*)-1-(4-Nitrophenyl)-2-nitroethanol 7k

91% Yield, 53% ee; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 90:10 v/v, 1 mL/min, 23 °C, UV = 214 nm): t_r(minor) = 14.4 min, t_r(major) = 17.9 min; $[\alpha]_D^{25} = +18.6$ (*c* 0.68, CH_2Cl_2, 53% ee). ^1H NMR (400 MHz, $CDCl_3$): δ 8.20–8.22 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 2H), 5.60 (m, 1H), 4.54–4.62 (m, 2H), 3.43 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.0, 145.1, 127.0, 124.0, 80.5, 69.9; MS (EI): *m*/*z* 212 [M^+].

4.6.12. (*S*)-1-(2-Nitrophenyl)-2-nitroethanol 7l

85% Yield, 81% ee; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 90:10 v/v, 1.0 mL/min, 23 °C, UV = 214 nm): t_r(minor) = 10.2 min, t_r(major) = 11.1 min; $[\alpha]_D^{25} = -189.8$ (*c* 0.58, CH_2Cl_2, 81% ee). ^1H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.6 Hz, 1H); 7.94 (d, *J* = 7.7 Hz, 1H), 7.73 (t, *J* = 7.7 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 1H), 6.02 (d, *J* = 9.6 Hz, 1H), 4.85 (dd, *J* = 12.5, 1.9 Hz, 1H), 4.51 (dd, *J* = 13.5, 4.8 Hz, 1H), 3.30 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.1, 134.3, 134.0, 129.6, 128.6, 125.0, 80.0, 66.7; MS (EI): *m*/*z* 212 [M^+].

4.6.13. (*S*)-1-(1-Naphthyl)-2-nitroethanol 7m

78% Yield, 81% ee; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 85:15 v/v, 1 mL/min, 23 °C, UV = 215 nm): t_r(minor) = 14.6 min, t_r(major) = 19.6 min; $[\alpha]_D^{25} = +15.4$ (*c* 0.98, CH_2Cl_2, 81% ee). ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.61–7.50 (m, 3H), 6.30–6.28 (m, 1H), 4.71–4.65 (m, 2H), 3.07 (d, *J* = 2.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.7, 133.5, 129.5, 129.4, 129.3, 127.0, 126.1, 125.4, 123.8, 121.8, 80.8, 68.3; MS (EI): *m*/*z* 217 [M^+].

4.6.14. (*S*)-1-Nitropentan-2-ol 7n

75% Yield, 77% ee; HPLC (Chiralcel OD-H, *n*-hexane/*i*-PrOH, 98:2 v/v, 0.6 mL/min, 23 °C, UV = 215 nm): t_r(minor) = 33.5 min, t_r(major) = 35.4 min; $[\alpha]_D^{25} = +12.2$ (*c* 0.2, $CHCl_3$, 77% ee). ^1H NMR (300 MHz, $CDCl_3$): δ 4.51–4.36 (m, 2H), 4.44–4.32 (m, 1H), 2.89–2.70 (br s, 1H), 1.65–1.27 (m, 4H), 1.02 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 80.8, 68.6, 35.8, 18.5, 13.8; MS (EI): *m*/*z* 133 [M^+].

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