Tetrahedron: *Asymmetry* 22 (2011) 1169–1175

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

Enantioselective Henry reaction catalyzed by a copper(II) *gluco*BOX complex

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ARTICLE INFO

Article history:
Received 16 May 2011
Accepted 8 June 2011
Available online 27 July 2011

ABSTRACT

A highly enantioselective Henry reaction has been developed using a chiral copper(II)–*gluco*BOX complex. The catalytic system works well with a wide range of aromatic, aliphatic and heteroaromatic aldehydes to afford the corresponding nitroalkanols with high enantioselectivity (up to 99%) in excellent yields (up to 95%). The catalyst shows good enantioselectivity with 10 mol % of loading at easily attainable temperature (10 °C) even in the absence of an inert atmosphere.

1. Introduction

The Henry reaction is a powerful synthetic tool for the stereoselective construction of carbon–carbon bonds.[1] The enantioselective version of this reaction is highly important because the resulting chiral 2-nitro-1-alkanols are versatile intermediates for the synthesis of biologically active molecules[2] and can be easily transformed into β-amino alcohols by reduction and α-hydroxy ketones or carboxylic acids by a Nef reaction.[3] The catalytic enantioselective nitroaldol reaction still has some problems, such as high catalyst loading[4] and the necessity of activation of the nitroalkane to a silyl nitronate.[5] Therefore, the development of a catalytic asymmetric version of the Henry reaction is of prime importance.

Several chiral metal complexes have been developed for the enantioselective Henry reaction,[6] especially of aromatic aldehydes. However, the enantioselective nitroaldol reaction of aliphatic aldehydes remains less explored. Most enantioselective Henry reactions have been reported either with chiral copper catalysts or with chiral zinc catalysts. Chiral copper complexes show high enantioselectivities and yields under mild reaction conditions. Chiral zinc catalysts[4] were also found to be equally effective for asymmetric Henry reactions but these reactions of chiral zinc complexes need to be carried out under strictly dry conditions which limit their use in large scale synthesis. Chiral ligands such as bisoxazolines,[7] sparteine,[8] chiral diamines,[9] bisoxazolidines,[10] *N*-oxides,[11] sulfonamides,[12] BoroBox,[13] aminopyrineligands,[14] bispidine,[15] sulfonamides diamine[16] and chiral sulfoximines[17] have been utilized with the advantage of excellent coordination of copper with these nitrogen containing bidentate ligands. A copper-pyridine bis(imidazoline)[18] complex was also found to catalyze the reaction with excellent enantioselectivity. Recently, per-6-amino functionalized β-cyclodextrin[19] was used as a chiral host for enantioselective Henry reaction. Apart from the different catalytic systems mentioned above, some other metals such as chromium[20] and cobalt[21] complexes have also afforded good results.

Carbohydrates are well known chiral building blocks for the synthesis of a wide range of biologically active molecules but the use of carbohydrates in asymmetric synthesis remains less explored. A few carbohydrate derived ligands[22] have recently been developed and applied for a few enantioselective reactions such as alkynylations,[23] hydrovinylations[24] and hydrogenations.[25] Glucosamine derived bis(oxazoline)[26] and pyridine bis(oxazoline) ligands[27] are noteworthy for the enantioselective cyclopropanation and alkynylation of imines, respectively. Inspired by the success of exploring the sugar based bis(oxazoline) ligands by Boysen et al., we became interested in examining the reactivity of *gluco*BOX in enantioselective Henry reaction.

Herein, we report for the first time the enantioselective Henry reaction of a variety aldehydes with nitroalkanes by employing copper(II) complexes of a glucosamine based bis(oxazoline) ligand. The chiral copper(II)-bis(oxazoline) complex was prepared in situ from *gluco*BOX and $Cu(OAc)_2 \cdot H_2O$ in EtOH at room temperature. The sugar based bis(oxazoline), that is, *gluco*BOX was prepared from glucosamine and dimethyl malonyl chloride using a known procedure.[26a] The *gluco*BOX ligands have almost similar skeleton in comparison to *inda*BOX ligands (Fig. 1).

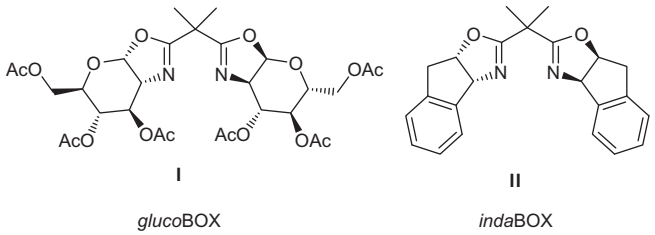

Figure 1. Structures of *gluco*BOX and *inda*BOX ligands.

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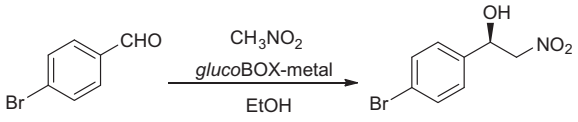
doi:10.1016/j.tetasy.2011.06.012

Table 1
Screening of various reaction parameters in the enantioselective Henry reaction of 4-bromobenzaldehyde with nitromethane catalyzed by copper(II)-*gluco*BOX



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Entry	Lewis acid	Catalyst(mol %)	Solvent[a]	T (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	$Cu(OAc)_2$	10	EtOH	25	15	88	73
2	$Cu(OAc)_2$	10	MeOH	25	15	86	68
3	$Cu(OAc)_2{\cdot}H_2O$	10	EtOH	25	15	88	76
4	$Cu(OAc)_2{\cdot}H_2O$	10	EtOH	25	15	90	78
5	$Cu(OAc)_2{\cdot}H_2O$	10	THF	25	15	60	55
6	$Cu(OAc)_2{\cdot}H_2O$	10	DMF	25	15	75	27
7	$Cu(OAc)_2{\cdot}H_2O$	10	CH_2Cl_2	25	15	45	12
8	$Cu(OAc)_2{\cdot}H_2O$	10	Toluene	25	15	45	12
9	$Cu(OTf)_2$+Et_3N	10	EtOH	25	10	80	20
10	$CuCl_2$+Et_3N	10	EtOH	25	10	84	16
11	$Zn(OTf)_2$+Et_3N	10	EtOH	25	10	71	27
12	$Cu(OAc)_2{\cdot}H_2O$	10	EtOH	0	55	45	86
13	$Cu(OAc)_2{\cdot}H_2O$	10	EtOH	−20	90	10	n.d.
14	$Cu(OAc)_2{\cdot}H_2O$	10	EtOH	10	40	83	89
15	$Cu(OAc)_2{\cdot}H_2O$	5		10	40	77	86
16	$Cu(OAc)_2{\cdot}H_2O$	20	EtOH	10	40	84	89
17[d]	$Cu(OAc)_2{\cdot}H_2O$	10	EtOH	10	40	84	88
18[e]	$Cu(OAc)_2{\cdot}H_2O$	10	EtOH	10	40	85	86

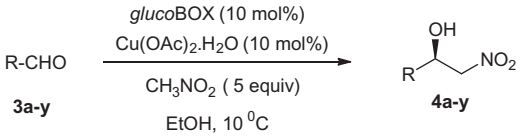
[a] All reactions were carried out with 5 equiv, of nitromethane.
[b] Yield refers to pure products after chromatography.
[c] Enantiomeric excess was determined by chiral HPLC.
[d] 10 equiv, of nitromethane was used.
[e] Reaction was carried out with 2 equiv of nitromethane.

2. Results and discussion

On the basis of previous studies on the copper catalyzed enantioselective Henry reaction, our first attempt was to carry out the enantioselective Henry reaction using different copper salts as catalysts. Copper acetate was already known as a very good catalyst for the enantioselective Henry reaction in the absence of any base or additive. From this general observation, we began our study with 4-bromobenzaldehyde and nitromethane as a model reaction using an in situ generated Cu(II)-chiral complex from anhydrous $Cu(OAc)_2$ and *gluco*BOX in ethanol under strictly anhydrous conditions. Although the reaction proceeded smoothly in good yield (90%), the ee was not so impressive (73%) (Table 1, entry 1). Next, we attempted the same reaction with a $Cu(OAc)_2.H_2O$-*gluco*BOX complex at room temperature under a nitrogen atmosphere. There was no considerable difference in yield, but a slight increase in enantioselectivity (76%) was observed (Table 1, entry 3). Next, we performed the reaction with $Cu(OAc)_2.H_2O$-*gluco*BOX in the absence of a nitrogen atmosphere. Under these conditions, the enantioselectivity increased again to 78% (Table 1, entry 4). We also attempted the reaction using a $Cu(OAc)_2.H_2O$-*gluco*BOX complex as a catalyst in different solvents, but none of them gave a higher ee than EtOH (Table 1).

We next attempted to find the best metal for the enantioselective Henry reaction (Table 1, entries 9–11). However, no other metal complex was found to give better results than $Cu(OAc)_2.H_2O$. From the above observations, we found that $Cu(OAc)_2.H_2O$ in EtOH was the best choice for the present study. Accordingly, we tried to optimize the reaction by varying the temperature from −20 °C to 25 °C. A maximum enantiomeric excess was achieved at 10 °C without affecting the yield (Table 1, entry 14). At low temperature, for example, below to 0 °C, the reaction was too slow to afford the product in a reasonable yield (Table 1, entry 12). The enantioselectivity also slightly decreased when decreasing the reaction temper-

Table 2
Enantioselective Henry reaction of aldehydes catalyzed by a $Cu(OAc)_2.H_2O$-*gluco*BOX complex in EtOH



3a-y 4a-y

Entry	R	Product[a]	Time[b] (h)	Yeild (%)[c]	ee (%)[d]
1	Ph-(**3a**)	**4a**	40	85	94
2	4-Cl-C_6H_4-(**3b**)	**4b**	40	93	92
3	4-F-C_6H_4-(**3c**)	**4c**	40	88	90
4	4-NO_2-C_6H_4-(**3d**)	**4d**	40	79	83
5	4-CH_3-C_6H_4-(**3e**)	**4e**	40	82	91
6	4-MeO-C_6H_4-(**3f**)	**4f**	40	78	90
7	2-Br-C_6H_4-(**3g**)	**4g**	40	84	89
8	2-NO_2-C_6H_4-(**3h**)	**4h**	40	88	91
9	2-MeO-C_6H_4-(**3i**)	**4i**	40	82	90
10	2-Cl,4-F-C_6H_3-(**3j**)	**4j**	40	88	90
11	2,4-Cl_2-C_6H_4-(**3k**)	**4k**	40	84	89
12	3,4-$(MeO)_2$-C_6H_3-(**3l**)	**4l**	40	81	89
13	2,5-$(MeO)_2$-C_6H_3-(**3m**)	**4m**	40	84	99
14	3,4,5-$(MeO)_3$-C_6H_2 (**3n**)	**4n**	40	80	90
15	1-Naphthyl-(**3o**)	**4o**	40	78	90
16	2-Naphthyl-(**3p**)	**4p**	40	95	90
17	$CH_3(CH_2)_2$-(**3q**)	**4q**	40	85	77
18	$CH_3(CH_2)_4$-(**3r**)	**4r**	40	55	84
19	$CH_3(CH_2)_7$-(**3s**)	**4s**	40	46	82
20	$(CH_3)_2CHCH_2$-(**3t**)	**4t**	40	63	82
21	2-Thiophenyl-(**3u**)	**4u**	40	88	92
22	2-Furyl-(3v)	**4v**	40	93	90
23	*trans*-Cinnamyl-(**3w**)	**4w**	40	72	85

[a] All reactions were performed with 0.5 mmol of aldehyde and 5 equiv of nitromethane at 10 °C.
[b] Catalyst loading was 10 mol % with respect to aldehyde.
[c] Yield was determined after chromatography.
[d] Ee was deteremined by HPLC using chiracel OD-H, AD-H or OJ-H columns using a mixture of hexane-isopropyl alcohol as eluent.

ature to 0 °C. By decreasing the temperature to below −20 °C, the reaction was sluggish and the yield was very low (Table 1, entry 13). To optimize the catalyst loading, the reaction was carried out with different amounts of the catalyst and we found that 10 mol % of the catalyst was required to give the best results (Table 1, entry 14). The effect of various equivalents of nitromethane was studied, (Table 1, entries 16–18) the best results were obtained when 5 equiv of nitromethane were used (Table 1, entry 16).

Next, the scope of the asymmetric Henry reaction was studied with various aldehydes using this *gluco*BOX ligand (Table 2). Initially, we tested the reactivity of benzaldehyde under the optimized reaction conditions. The corresponding 2-nitro-1-phenylethanol was obtained in 85% yield with 94% ee (Table 2, entry 1). Then *para*-substituted benzaldehydes bearing electron donating and electron withdrawing groups were investigated. All *para*-substituted aryl aldehydes gave almost similar enantioselectivities (Table 2, entries 2–6). Among these, low enantioselectivity was obtained with 4-nitrobenzaldehyde (Table 2, entry 4). The lower enantioselectivity of 4-nitrobenzaldehyde may be due to the coordinating ability of the nitro group. Similarly, *p*-anisaldehyde also gave the product in low yield (78%, Table 2, entry 6). This is due to the electron donating ability of methoxyl group by which the electron density increases slightly at carbonyl carbon which diminishes the reactivity of carbonyl group.

To understand the influence of steric factors, several *ortho*-substituted benzaldehydes were examined (Table 2, entries 7–9). In general, *ortho*-substituted aldehydes gave almost similar yields and enantioselectivities irrespective of their nature. For example, *o*-anisaldehyde gave the same ee as *p*-anisaldehyde, but the yield was slightly higher than with *p*-anisaldehyde (Table 2, entry 9). However, *o*-bromobenzaldehyde did not show any significant effect on the enantioselectivity (Table 2, entry 7).

A set of disubstituted benzaldehydes bearing electron donating and electron withdrawing groups were studied (Table 2, entries 10–14). Almost all disubstituted benzaldehydes gave similar enantioselectivities with slight variations in yields. It is noteworthy that 2,5-dimethoxybenzaldehyde gave excellent enantioselectivity (>99%) (Table 2, entry 13). The more sterically crowded 3,4,5-trimethoxybenzaldehyde also gave good enantioselectivity (90%) and good yield (80%) (Table 2, entry 14).

Similarly, the sterically hindered - and -naphthaldehydes gave the nitroaldols with good enantioselectivity without any significant difference in yields (Table 2, entries 15 and 16).

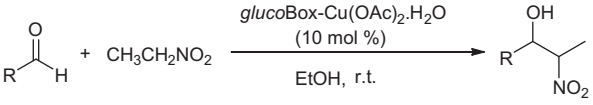
Inspired by the good results obtained with the aromatic aldehydes, we next attempted the Henry reaction with some aliphatic aldehydes (Table 2, entries 17–20). However, all aliphatic aldehydes gave lower yields and enantioselectivities compared to the aromatic substrates. In the cases of non-branched aliphatic aldehydes, the yield decreased with an increase of the chain length (Table 2, entry 17 and 18). For instance, butyraldehyde gave higher yield than other aliphatic aldehydes in our study. The highest ee of 84% was obtained with *n*-hexanal (Table 2, entry 18). However, the enantioselectivity remains almost the same even when increasing the chain length of the aldehydes.

In addition to the aromatic and aliphatic substrates, the reactivity of the heteroaromatic aldehydes was also examined. Both thiophene-2-carboxaldehyde and 2-furfuraldehyde gave excellent yields and enantioselectivities (Table 2, entries 21 and 22). Thiophene-2-carboxaldehyde gave slightly higher ee (92%), but a higher yield was obtained with 2-furfuraldehyde. *trans*-Cinnamaldehyde also gave the nitroaldol with high enantioselectivity (85%) and in good yield (72%) (Table 2, entry 23).

Finally, we attempted the diastereoselective Henry reaction of aldehydes with nitroethane (Table 3). The diastereoselective nitroaldol reactions were too sluggish at 10 °C, hence these reactions were carried out at room temperature. Although the reactions proceeded smoothly at room temperature, the corresponding nitroalkanols were only obtained in moderate yields with good diastereoselectivity (Table 3, entries 1 and 2). The enantioselectivity and diasterimeric ratio were very high when 4-chlorobenzaldehyde was treated with nitroethane at 10 °C (Table 3, entry 3). 4-Chlorobenzaldehyde gave excellent diastereoselectivity (13:1, favoring the *anti*-isomer). Due to the low conversions and extended reaction times, the diastereoselective Henry reaction of higher nitroalkanes was not studied under similar conditions. Some of the selected examples are shown in Table 3.

From the aforementioned observations, we attempted to propose a mechanism for the enantioselective nitroaldol reaction. We assumed that the structure of the copper(II)-*gluco*BOX complex possesses two strongly co-ordinating sites almost in a ligand plane. Due to Jahn-Teller distortion, two weakly co-ordinating sites are available in a plane perpendicular to the ligand plane. In the transition state, the aldehyde co-ordinates to the copper complex and the nitromethane was activated by free acetate ion which is generated when aldehyde co-ordinates with copper(II)-*gluco*BOX. The activated nitromethane may be binding with copper(II)-*gluco*BOX as shown in Figure 2. In the transition state, acetate groups of ligands are crowding around the aldehyde and nitromethane moiety. The acetate groups orient each other in opposite direction with respect to its neighboring one. The sterric factors may be a strong reason why the reaction is very slow at low temperature. The low reactivity of nitroethane under standard conditions (at 10 °C) may be due to the same steric effect.

Table 3
Diastereoselective Henry reaction of nitroethane with aldehydes catalyzed by $Cu(OAc)_2.H_2O$-*gluco*BOX



Entry	R	Product[a]	Time (h)[b,c]	Yield (%)[d]	(*anti*/*syn*)	ee[e] (%) (*anti*/*syn*)
1	2-NO_2-C_6H_4–	**5a**	72	60	2.1/1	68/73
2	3,4-Cl-C_6H_3–	**5b**	75	65	2.0/1	86/71
3	4-Cl-C_6H_4–	**5c**	60	75	13/1	80/62

[a] All reactions were performed with 0.5 mmol of aldehyde in 2 mL EtOH and with 5 equiv of nitroethane.
[b] All reactions were carried out at 25 °C except entry 3(10 °C).
[c] Catalyst loading was 10 mol % with respect to aldehyde.
[d] Yield was determined after chromatography.
[e] Ee was determined by HPLC using chiracel AD-H column using a mixture of hexane and isopropanol as eluent.

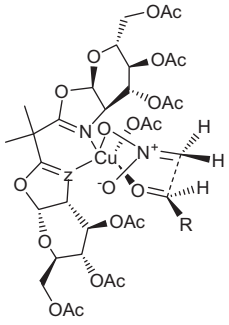


Figure 2. Transition state model for enantioselective Henry reaction catalyzed by copper(II)-*gluco*BOX.

3. Conclusion

In conclusion, we have demonstrated a highly enantioselective nitroaldol (Henry) reaction of aldehydes using a chiral Cu(II)-*gluco*BOX complex under mild reaction conditions. This method is simple and convenient for the synthesis of a variety of nitroalkanols in high yields and enatioselectivity. This method provides high yields of nitroalkanols (up to 95%) with excellent enantioselectivities (up to >99%) at low catalyst loading (10 mol %). This chiral complex works well for both aromatic and aliphatic substrates at a practical temperature (10 °C) even in the absence of an inert atmosphere.

4. Experimental

4.1. General remarks

All chemicals were purchased commercially and were used without any further purification. All solvents used were purchased commercially and purified according to standard procedures. All nitroalkanols were purified by column chromatography on Silica gel (60–120 mesh) using hexane–ethyl acetate mixture as eluent. 2-Furaldehyde and cinnamaldehyde were purified by column chromatography on alumina prior to use, and all other aldehydes were used as received. All nitroalkanols were characterized by NMR spectroscopy. The ^{1}H NMR spectra of all nitroalkanols were recorded on either 200 MHz or 300 MHz or 500 MHz instruments using TMS as an internal standard in $CDCl_3$. The ^{13}C NMR spectra of all products were recorded on either 75 MHz or 50 MHz instruments using $CDCl_3$ as solvent and reference. The enantiomeric excesses of all products were determined by HPLC analysis using Chiracel AD-H, OD-H and OJ-H columns using hexane-isopropyl alcohol mixtures as eluent. The absolute configurations of all products were determined by comparing specific rotations of the nitroalkanols with known compounds or/and by comparison with analogs or/and by comparison of retention times in HPLC analysis with literature data (*Note*: all the HPLC analysis were done based on previous HPLC conditions reported in the literature included as reference).

4.2. General procedure for the enantioselective Henry reaction of aldehyde with nitromethane

A solution of *gluco*BOX[26a] (35 mg, 0.052 mmol) and Cu(OAc)$_2$.H$_2$O (10 mg, 0.05 mmol) in ethanol (2 mL) was stirred at room temperature for 1 h. To this blue colored solution, the aldehyde (0.5 mmol) was added and the resulting solution was allowed to stir for 20 min at room temperature. The reaction mixture was cooled to 10 °C and then nitromethane (5 equiv) was added. The resulting mixture was stirred at the same temperature for a specified time (Table 1). The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel to afford the pure nitroalkanol.

4.2.1. (*R*)-1-(4-Bromophenyl)-2-nitroethanol[10] 4 (Table 1, entry 10)

Yield 83%; Enantiomeric excess: 89%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.02 (s, 1H), 4.40 (dd, J = 3.6, 13.6 Hz, 1H), 4.47 (dd, J = 8.8, 13.4 Hz, 1H), 5.36 (d, J = 8.1 Hz, 1H), 7.24 (d, J = 8.3 Hz, 2H), 7.48 (d, J = 8.3 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 70.1, 807, 122.5, 127.4, 131.8, 136.9; HPLC Analysis: Chiracel OD-H column (85:15, *n*-hexane–isopropyl alcohol, 0.8 mL/min, 215 nm); t_R = 12.25 min (major, (*R*)-isomer); t_R = 15.62 min (minor, (*S*)-isomer); $[\alpha]_D^{20} = -68.6$ (*c* 1.5, CH_2Cl_2).

4.2.2. (*R*)-2-Nitro-1-phenylethanol[7a] 4a (Table 2, entry 1)

Yield 85%; Enantiomeric excess 94%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.50 (s, 1H), 4.34 (dd, J = 3.8, 13.6 Hz, 1H), 4.44 (dd, J = 9.1, 12.8 Hz, 1H), 5.30 (dd, J = 3.8, 9.8 Hz, 1H), 7.22 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 70.6, 80.8, 125.7, 128.5, 128.6, 138.1; HPLC Analysis: Chiracel OD-H column (85:15, *n*-hexane–isopropyl alcohol, 0.8 mL/min, 215 nm); t_R = 11.54 min (major, (*R*)-isomer); t_R = 13.18 min (minor, (*S*)-isomer); ee 94%; $[\alpha]_D^{20} = -42.6$ (*c* 1.0, CH_2Cl_2).

4.2.3. (*R*)-1-(4-Chlorophenyl)-2-nitroethanol[7a] 4b (Table 2, entry 2)

Yield 93%; Enantiomeric excess 92%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.20 (s, 1H), 4.40 (dd, J = 3.8, 13.6 Hz, 1H), 4.60 (dd, J = 9.1, 13.6 Hz, 1H), 5.36 (dd, J = 3.0, 9.1 Hz, 1H), 7.28 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 70.1, 80.9, 127.2, 128.983, 134.5, 136.6; HPLC Analysis: Chiracel OD-H column (85:15, *n*-hexane–isopropyl alcohol, 0.8 mL/min, 215 nm); t_R = 11.72 min (major, (*R*)-isomer); t_R = 15.62 min (minor, (*S*)-isomer); ee 92%; $[\alpha]_D^{20} - 38.1$ (*c* 1, CH_2Cl_2).

4.2.4. (*R*)-1-(4-Fluorophenyl)-2-nitroethanol[7a] 4c (Table 2, entry 3)

Yield 88%; Enantiomeric excess 90%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.10 (s, 1H), 4.40 (dd, J = 3.8, 13.6 Hz, 1H), 4.46 (dd, J = 9.1, 12.8 Hz, 1H), 5.38 (dd, J = 3.0, 9.1 Hz, 1H), 7.02 (m, 2H), 7.34 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 70.1, 81.0, 115.6, 11.9, 127.7, 134.0, 161.0, 164.3; HPLC Analysis: Chiracel OD-H column (90:10, *n*-hexane–isopropyl alcohol, 1.0 mL/min, 215 nm); t_R =11.30 min (major, (*R*)-isomer); t_R =13.39 min (minor, (*S*)-isomer); ee 90%; $[\alpha]_D^{20} = -42.9$ (*c* 0.99, CH_2Cl_2).

4.2.5. (*R*)-2-Nitro-1-(4-nitrophenyl)ethanol[7a] 4d (Table 2, entry 4)

Yield 79%; enantiomeric excess 83%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.24 (s, 1H), 4.52 (m, 2H), 5.55 (m, 1H), 7.58 (d, J = 8.7 Hz, 2H), 8.24 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 69.9, 80.6, 124.0, 126.9, 145.3, 147.9; HPLC Analysis: Chiracel OD-H column (85:15, *n*-hexane–isopropyl alcohol, 0.7 mL/min, 254 nm); t_R = 18.43 min (major, (*R*)-isomer); t_R = 23.32 min (minor, (*S*)-isomer); ee 83%; $[\alpha]_D^{20} = -33.6$ (*c* 1.1, CH_2Cl_2).

4.2.6. (*R*)-2-Nitro-1-*p*-tolylethanol[9e] 4e (Table 2, entry 5)

Yield 82%, enantiomeric excess 91%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 1H), 2.90 (s, 1H), 4.36 (dd, J = 3.2, 13.2 Hz, 1H), 4.48 (dd, J = 9.4, 13.2 Hz, 1H), 5.30 (d, J = 9.2 Hz, 1H), 7.12 (d, J = 7.9 Hz, 2H), 7.20 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.9, 70.6, 80.9, 125.7, 129.4, 135.1, 138.5; HPLC Analysis: Chiracel OD-H column (90:10, *n*-hexane–isopropyl alcohol, 0.7 mL/min, 254 nm); t_R = 18.16 min (major, (*R*)-isomer); t_R = 23.31 min (minor, (*S*)-isomer); ee 91%; $[\alpha]_D^{20} = -44.3$ (*c* 1.0, CH_2Cl_2).

4.2.7. 4.3.7(*R*)-1-(4-Methoxyphenyl)-2-nitroethanol[8]. 4f (Table 2, entry 6)

Yield 78%, enantiomeric excess 90%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.10 (s, 1H), 3.90 (s, 3H), 4.54 (dd, J = 2.9, 13.7 Hz, 1H), 4.64 (dd, J = 9.8, 13.7 Hz, 1H), 5.46 (dd, J =2.9, 9.8 Hz, 1H), 7.05 (d, J = 7.8 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 55.3, 70.6, 114.3, 127.2, 130.2, 159.9. HPLC Analysis: Chiracel OD-H column (85:15, *n*-hexane–isopropyl alcohol, 0.8 mL/min, 215 nm); t_R = 15.713 min (major, (*R*)-isomer); t_R = 19.826 min (minor, (*S*)-isomer); ee 94%; $[\alpha]_D^{20} = -31.9$ (*c* 0.9, CH_2Cl_2).

4.2.8. (*R*)-1-(2-Bromophenyl)-2-nitroethanol[9e] 4g (Table 2, entry 8)

Yield 84%, enantiomeric excess 89%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.06 (s, 1H), 4.30 (dd, J = 9.6, 13.8 Hz, 1H), 4.64 (dd, J = 1.9,

13.8 Hz, 1H), 5.70 (d, J = 9.6 Hz, 1H), 7.15 (m, 1H), 7.35 (t, J = 7.4 Hz, 1H), 7.50 (d, J = 7.9 Hz, 1H). 7.64 (d, J = 7.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 69.8, 79.2, 121.2, 127.6, 128.0, 130.0, 132.7, 137.1. HPLC Analysis: Chiracel OD-H column (95:15, *n*-hexane–isopropyl alcohol, 0.6 mL/min, 215 nm); t_R = 23.497 min (major, (*R*)-isomer); t_R = 25.691 min (minor, (*S*)-isomer); ee 89%; $[\alpha]_D^{20} = -35.2$ (*c* 1.0, CH_2Cl_2).

4.2.9. (*R*)-2-Nitro-1-(2-nitrophenyl)ethanol[8] 4h (Table 2, entry 9)

Yield 88%, enantiomeric excess 91%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.28 (s, 1H), 4.44 (dd, J = 9.1, 14.4 Hz, 1H), 4.82 (dd, J =3.0, 14.4 Hz, 1H), 5.98 (d, J = 9.6 Hz, 1H), 7.50 (m, 1H), 7.68 (m, 1H), 7.94 (d, J = 6.8 Hz, 1H). 8.4 (d, J = 8.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 66.6, 80.0, 124.8, 128.6, 129.5, 134.2, 134.3, 146.9. HPLC Analysis: Chiracel OD-H column (90:10, *n*-hexane–isopropyl alcohol, 0.9 mL/min, 215 nm); t_R = 16.014 min (major, (*R*)-isomer); t_R = 17.838 min (minor, (*S*)-isomer); ee 91%; $[\alpha]_D^{20} = -222.3$ (*c* 1.0, CH_2Cl_2).

4.2.10. (*R*)-1-(2-Methoxyphenyl)-2-nitroethanol[7a] 4i (Table 2, entry 10)

Yield 82%, enantiomeric excess 90%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.30 (s, 1H), 3.84 (s, 3H), 4.40 (dd, J = 10.0, 13.7 Hz, 1H), 4.54 (dd, J = 2.7, 12.8 Hz, 1H), 5.53 (d, J = 8.2 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 6.92 (t, J = 7.3 Hz, 1H). 7.22 (m, 1H), 7.38 (d, J = 7.3 Hz, 1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 67.6, 79.8, 110.4, 121.0, 125.9, 127.1, 129.7, 155.9. HPLC Analysis: Chiracel OD-H column (90:10, *n*-hexane–isopropyl alcohol, 0.8 mL/min, 215 nm); t_R = 13.09 min (major, (*R*)-isomer); t_R = 15.746 min (minor, (*S*)-isomer); ee 94%; $[\alpha]_D^{25} = -44.0$ (*c* 1.1, CH_2Cl_2).

4.2.11. (*R*)-1-(2-Chloro-4-fluorophenyl)-2-nitroethanol 4j: (Table 2, entry 11)

Yield 88%; enantiomeric excess 90%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.12 (s, 1H), 4.32 (dd, J = 9.8, 13.6 Hz, 1H), 4.58 (dd, J = 2.7, 13.6 Hz, 1H), 5.74 (dd, J = 1.5, 9.8 Hz, 1H), 7.14 (m, 2H), 7.64 (dd, J = 6.0, 8.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 67.3, 79.3, 114.8 (d, J = 20.9 Hz), 117.3 (d, J = 24.7 Hz), 128.8 (d, J = 9.3 Hz), 131.5 (d, J = 2.7 Hz), 132.2 (d, J = 9.8 Hz), 160.8 (d, J = 251.9 Hz). HRMS (ESI) calcd for $C_9H_9ClFNO_3Na$, 241.9991, found, 241.9988. HPLC Analysis: Chiracel AD-H column (90:10, *n*-hexane–isopropyl alcohol, 0.5 mL/min, 215 nm); t_R = 17.791 min (major, (*R*)-isomer); t_R = 21.054 min (minor, (*S*)-isomer); ee 90%; $[\alpha]_D^{20} = -82.3$ (*c* 1.46, $CHCl_3$).

4.2.12. (*R*)-1-(2,4-Dichlorophenyl)-2-nitroethanol[28] 4k: (Table 2, entry 12)

Yield 84%, enantiomeric excess 89%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.28 (s, 1H), 4.282 (dd, J = 10.1, 14.3 Hz, 1H), 4.56 (dd, J = 2.5, 13.4 Hz, 1H), 5.68 (d, J = 9.2 Hz, 1H), 7.28 (m, 2H), 7.58 (d, J = 8.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 67.4, 79.1, 127.9, 128.5, 129.5, 132.0, 134.2, 135.2. HPLC Analysis: Chiracel AD-H column (90:10, *n*-hexane–isopropyl alcohol, 0.5 mL/min, 215 nm); t_R = 17.683 min (major, (*R*)-isomer); t_R = 21.153 min (minor, (*S*)-isomer)[29]; ee 89%; $[\alpha]_D^{20} = -51.1$ (*c* 1, CH_2Cl_2).

4.2.13. (*R*)-1-(3,4-Dimethoxyphenyl)-2-nitroethanol 4l: (Table 2, entry 13)

Yield 81%, enantiomeric excess 89%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.84 (s, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 4.38 (dd, J = 3.0, 13.0 Hz, 1H), 4.48 (dd, J = 9.4, 13.2 Hz, 1H), 5.30 (d, J = 9.3 Hz, 1H), 6.78 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.9, 70.8, 81.3, 108.7, 111.2, 118.3, 130.7, 149.3. HPLC Analysis: Chiracel OD-H column (85:15, *n*-hexane–isopropyl alcohol, 1.0 mL/min, 254 nm); t_R = 26.97 min (major, (*R*)-isomer); t_R = 36.20 min (minor, (*S*)-isomer); ee 89%; $[\alpha]_D^{25} = -24.6$ (*c* 1, CH_2Cl_2).

4.2.14. (*R*)-1-(2,5-Dimethoxyphenyl)-2-nitroethanol[30] 4m: (Table 2, entry 14)

Yield 84%, enantiomeric excess 99%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.02 (d, J = 5.5 Hz, 1H), 3.76 (s, 3H), 3.82 (s, 3H), 4.38 (dd, J = 9.4, 13.4 Hz, 1H), 4.58 (dd, J = 2.6, 13.2 Hz, 1H), 5.54 (m, H), 6.76 (d, J = 1.5 Hz, 2H), 7.02(s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.8, 67.7, 79.8, 111.4, 113.1, 114.2, 126.9, 149.9, 153.9. HPLC Analysis: Chiracel OD-H column (85:15, *n*-hexane–isopropyl alcohol, 0.8 mL/min, 254 nm); t_R = 11.79 min (major, (*R*)-isomer); t_R = 13.97 min (minor, (*S*)-isomer); ee 99%; $[\alpha]_D^{20} = -36.6$ (*c* 1.0, $CHCl_3$).

4.2.15. (*R*)-2-Nitro-1-(3,4,5-trimethoxyphenyl)ethanol [9d] 4n (Table 2, entry 15)

Yield 80%, enantiomeric excess 90%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.16 (s, 1H), 3.76 (s, 3H), 3.82 (s, 6H), 4.38 (dd, J = 3.0, 13.0 Hz, 1H), 4.48 (dd, J = 9.4, 13.2 Hz, 1H), 5.28 (d, J = 8.9 Hz, 1H), 6.50 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.0, 60.8, 71.1, 81.3, 102.7, 134.1, 137.8, 153.4. HPLC Analysis: Chiracel OD-H column (85:15, *n*-hexane–isopropyl alcohol, 1.0 mL/min, 254 nm); t_R = 29.64 min (major, (*R*)-isomer); t_R = 38.55 min (minor, (*S*)-isomer); ee 90%; $[\alpha]_D^{20} = -23.6$ (*c* 1.1, CH_2Cl_2).

4.2.16. (*R*)-1-(Naphthalen-1-yl)-2-nitroethanol 4o (Table 2, entry 16)

Yield 78%, enantiomeric excess 90%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.12 (s, 1H), 4.48 (dd, J = 9.1, 13.6 Hz, H), 4.56 (dd, J = 3.0, 13.6 Hz, 1H), 6.14 (dd, J = 2.3, 9.1 Hz, 1H), 7.42 (m, 3H), 7.68 (d, J = 6.8 Hz, 1H), 7.76 (m, 2H), 7.94 (d, J = 8.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 67.9, 80.6, 121.7, 123.6, 125.3, 125.8, 126.7, 128.9, 129.3, 133.4, 133.6. HRMS (ESI) calcd for $C_{12}H_{11}NO_3$, 217.0739, found, 217.0744. HPLC Analysis: Chiracel OD-H column (90:10, *n*-hexane–isopropyl alcohol, 1.0 mL/min, 215 nm); t_R = 17.11 min (major, (*R*)-isomer); t_R = 25.57 min (minor, (*S*)- isomer); ee 90%; $[\alpha]_D^{20} = -24.6$ (*c* 1.0, CH_2Cl_2).

4.2.17. (*R*)-1-(Naphthalen-2-yl)-2-nitroethanol[28] 4p (Table 2, entry 17)

Yield 95%, enantiomeric excess 90%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.92 (s, 1H), 4.48 (dd, J = 3.0, 13.6 Hz, 1H), 4.58 (dd, J = 9.1, 13.6 Hz, 1H), 5.54 (m, 1H), 7.40 (m, 3H), 7.76 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 71.0, 51.1, 123.1, 128.2, 126.6, 127.6, 128.8, 133.0, 133.3, 135.3. HPLC Analysis: Chiracel OD-H column (80:20, *n*-hexane–isopropyl alcohol, 1.0 mL/min, 254 nm); t_R = 22.98 min (major, (*R*)-isomer); t_R = 32.50 min (minor, (*S*)-isomer); ee 90%; $[\alpha]_D^{20} = -14.6$ (*c* 1.0, CH_2Cl_2).

4.2.18. (*R*)-1-Nitropentan-2-ol[8] 4q (Table 2, entry 18)

Yield 85%, enantiomeric excess 77%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (t, J = 7.8 Hz, 3H), 1.38 (m, 2H), 1.48 (m, 2H), 2.74 (s, 1H), 4.24 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.3, 18.1, 35.5, 68.3, 80.6. HPLC Analysis: Chiracel OD-H column (98:02, *n*-hexane–isopropyl alcohol, 0.6 mL/min, 215 nm); t_R = 31.58 min (major, (*R*)-isomer); t_R = 34.93 min (minor, (*S*)-isomer); ee 77%; $[\alpha]_D^{20} = -15.2$ (*c* 2.1, CH_2Cl_2).

4.2.19. (*R*)-1-Nitroheptan-2-ol[28] 4r (Table 2, entry 19)

Yield 55%, enantiomeric excess 84%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, J = 6.8 Hz, 3H), 1.24 (m, 6H), 1.44 (m, 2H), 3.32 (s, 1H), 4.20 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6, 22.1, 24.6, 31.1, 33.5, 68.6, 80.5. HPLC Analysis: Chiracel AD-H column (98:02, *n*-hexane–isopropyl alcohol, 0.9 mL/min, 215 nm); t_R = 33.46 min (major, (*R*)-isomer); t_R = 48.94 min (minor, (*S*)-isomer); ee 84%; $[\alpha]_D^{20} = -8.5$ (*c* 2.5, CH_2Cl_2).

4.2.20. (*R*)-1-Nitrodecan-2-ol 4s[16] (Table 2, entry 20)

Yield 46%, enantiomeric excess 82%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84 (t, J = 7.3 Hz, 3H), 1.20 (m, 12H), 1.40 (m, 2H), 2.40 (s, 1H), 4.22 (m, 1H), 4.28 (dd, J = 8.2, 12.8 Hz, 1H), 4.36 (dd, J = 2.7, 12.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 22.6, 25.1, 29.1, 29.2, 29.3, 31.7, 33.7, 68.7, 80.6. HPLC Analysis: Chiracel AD-H column (95:05 *n*-hexane–isopropyl alcohol, 1.0 mL/min, 215 nm); t_R = 11.26 min (major, (*R*)-isomer); t_R = 16.83 min (minor, (*S*)-isomer); ee 82%; $[\alpha]_D^{20}$ = −4.5 (*c* 2.5, CH_2Cl_2).

4.2.21. (*R*)-4-Methyl-1-nitropentan-2-ol[7a] 4t (Table 2, entry 21)

Yield 63%, enantiomeric excess 82%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (t, J = 6 Hz, 6H), 1.22 (m, 1H), 1.47 (m, 1H), 1.80 (m, 1H), 3.38 (s, 1H), 4.35 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.4, 22.7, 23.9, 42.2, 66.9, 80.9. HPLC Analysis: Enantiomeric excess was determined by HPLC with Chiracel OJ-H column (95:05, *n*-hexane–isopropyl alcohol, 0.6 mL/min, 215 nm); t_R = 31.58 min (major, (*R*)-isomer); t_R = 34.93 min (minor, (*S*)-isomer); ee 82%; $[\alpha]_D^{20}$ = +2.3 (*c* 2.5, CH_2Cl_2).

4.2.22. (*S*)-2-Nitro-1-(thiophen-2-yl)ethanol[9c] 4u (Table 2, entry 23)

Yield 88%, enantiomeric excess 92%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.80 (s, 1H), 4.52 (dd, J =3.4, 13.4 Hz, 1H), 4.60 (dd, J = 9.1, 13.4 Hz, 1H), 5.62 (dd, J = 3.4, 9.0 Hz, 1H), 6.94 (m, 2H), 7.26 (dd, J = 1.1, 4.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 66.9, 80.7, 15.0, 126.0, 127.1, 141.3. HPLC Analysis: Chiracel OJ-H column (85:15, *n*-hexane–isopropyl alcohol, 0.8 mL/min, 215 nm); t_R = 26.21 min (major, (*S*)-isomer); t_R = 31.47 (minor, (*R*)-isomer); ee 92%; $[\alpha]_D^{20}$ = + 20.6 (*c* 0.25, CH_2Cl_2).

4.2.23. (S)-1-(Furan-2-yl)-2-nitroethanol[9c] 4v (Table 2, entry 24)

Yield 93%, enantiomeric excess 90%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.0 (s, 1H), 4.58 (dd, J = 3.8, 13.4 Hz, 1H), 4.66 (dd, J = 8.7, 13.4 Hz, 1H), 5.38 (dd, J = 3.8, 8.6 Hz, 1H), 6.34 (m, 2H), 7.36 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 64.7, 78.3, 108.1, 110.6, 143.1, 150.7. HPLC Analysis: Enantiomeric excess was determined by HPLC with Chiracel OJ-H column (90:10, *n*-hexane–isopropyl alcohol, 1.0 mL/min, 215 nm); t_R = 20.98 min (major, (*S*)-isomer); t_R = 25.29 (minor, (*R*)-isomer); ee 90%; $[\alpha]_D^{20}$ = −355.2 (*c* 0.25, CH_2Cl_2).

4.2.24. (*R,E*)-1-Nitro-4-phenylbut-3-en-2-ol[9c] 4w (Table 2, entry 25)

Yield 72%, enantiomeric excess 85%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.86 (s, 1H), 4.42 (d, J = 6.0 Hz, 2H), 4.94 (q, J = 6.0, 12.0 Hz, 1H), 6.02 (dd, J = 6.2, 15.8 Hz, 1H), 6.68 (d, J = 15.8 Hz, 1H), 7.22 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 69.4, 79.9, 125.4, 126.5, 128.1, 128.7, 32.9; HPLC Analysis: Chiracel OD-H column (85:15, *n*-hexane–isopropyl alcohol, 0.8 mL/min, 215 nm); t_R = 36.4 min (major, (*R*)-isomer); t_R = 31.9 (minor, (*S*)- isomer); ee 85%; $[\alpha]_D^{20}$ = −34.2 (*c* 1, CH_2Cl_2).

4.2.25. 2-Nitro-1-(2-nitrophenyl)propan-1-ol[9d] 5a (Table 3, entry 1)

Yield 60%; enantiomeric excess 68% (*anti*-isomer); enantiomeric excess 73% (*syn*-isomer). Diasteriomeric ratio 2.1:1 (*anti:syn*). Enantiomeric ratio and diasteriomeric ratio were determined by HPLC analysis. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (d, J = 7.6 Hz, 3H) (*anti*), 1.48 (d, J = 6.8 Hz, 1.4H) (*syn*), 3.40 (s, 1.2H)(*anti/syn*), 4.86 (dd, J = 6.8, 13.6 Hz, 1.4H) (*anti*), 5.62 (dd, J = 6.8 Hz, 0.5H) (*syn*), 6.02 (s, 1.0H) (*anti/syn*), 7.44 (m, 1.4H)(*anti/ syn*), 7.66 (m, 2H)(*anti/syn*), 7.88 (m, 1.4H) (*anti/syn*), 8.02 (d, J = 8.3 Hz, 0.9H)(*anti/syn*). HPLC Analysis: Chiracel AD-H column (90:10, *n*-hexane–isopropyl alcohol, 0.5 mL/min, 254 nm); t_R = 22.78 min (*anti*-minor); t_R = 24.59 (*anti*-major); ee 68% and t_R = 28.50 min (*syn*-minor); t_R = 37.78 (*syn*-major); ee 73% $[\alpha]_D^{20}$ = +106 (*c* 1.5, $CHCl_3$).

4.2.26. 1-(3,4-Dichlorophenyl)-2-nitropropan-1-ol 5b (Table 3, entry 2)

Yield 65%, enantiomeric excess 86% (*anti*=isomer); enantiomeric excess 71% (*syn*=isomer), diasteriomeric ratio 2.0:1 (*anti:syn*). Enantiomeric excess and diasteriomeric ratio were determined by HPLC analysis. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (d, J = 6.8 Hz, 0.8H) (*syn*), 1.44 (d, J = 6.8 Hz, 1.7H) (*anti*), 2.80 (s, 1H) (*anti/syn*), 4.46 (m, 1H) (*anti/syn*), 4.92 (d, J = 8.7 Hz, 0.3H) (*syn*), 5.34 (d, J = 2.5 Hz, 0.8H) (*anti*) 7.15 (m, 1.1H) (*anti/syn*), 7.42 (m, 2.1H)(*anti/syn*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.9 (*anti*), 16.3 (*syn*), 72.3 (*anti*), 74.9 (*syn*), 86.9 (*anti*), 87.9 (*syn*), 125.5 (*anti*), 126.1 (*syn*), 128.1 (*anti*), 128.9 (*syn*), 130.7 (*anti*), 130.9 (*syn*), 132.7 (*anti*), 133.1 (*anti*), 133.3 (*syn*), 133.4 (*syn*), 138.4 (*syn*), 138.5 (*anti*). Anal. calcd for $C_9H_9Cl_2NO_2$: C, 43.22; H, 3.63; N, 5.60. Found: C, 43.13; H, 3.45; N 5.50. HPLC Analysis**:** Chiracel AD-H column (90:10, *n*-hexane–isopropyl alcohol, 0.5 mL/min, 254 nm); t_R = 10.89 min (*anti* = major); t_R = 13.76 min (*anti*=minor); ee 86% and t_R = 15.67 min (*syn* = major); t_R = 22.79 min (*syn*=minor); ee 71% $[\alpha]_D^{20}$ = −21.8 (*c* 0.98, $CHCl_3$).

4.2.27. 1-(4-Chlorophenyl)-2-nitropropan-1-ol 5c[19] (Table 3, entry 3)

Yield 75%, enantiomeric excess 80% (*anti* isomer); enantiomeric excess 62% (*syn* isomer), diasteriomeric ratio 13:1 (*anti:syn*). Enantiomeric excess and diasteriomeric ratio were determined by HPLC analysis. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (d, J = 6.8 Hz, 0.6H) (*syn*), 1.44 (d, J = 6.8 Hz, 3.5H)(*anti*), 2.80 (s, 1.0H)(*anti/syn*), 4.56 (m, 1.0H)(*anti/syn*), 4.86 (d, J = 9.1 Hz, 0.3H)(*syn*), 5.34 (d, J = 3.0 Hz, 1.3H)(*anti*) 7.26 (m, 5.6H)(*anti/ syn*). HPLC Analysis: Chiracel AD-H column (95:05 *n*-hexane–isopropyl alcohol, 1.0 mL/min, 225 nm); t_R = 14.69 min (*anti* minor); t_R = 15.59 min (*anti* major); ee 80% and t_R = 20.85 min (*syn* major); t_R = 22.78 (*syn* minor); ee 60%. $[\alpha]_D^{20}$ -11.2 (*c* 0.6, $CHCl_3$).

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