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Supporting Information

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Enantioselective Henry Reactions Under Dual Lewis Acid/Amine Catalysis Using Chiral Amino Alcohol Ligands.**

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Angew. Chem.

General Information.

Nitroaldol reactions were carried out in screw cap round bottomed vials with magnetic stirring. Air and water were removed from the reaction vessel by flame and positive pressure of nitrogen. Nitromethane was used as received, the rest of solvents were dried and distilled following the general procedures. Zinc triflate ($Zn(OTf)_2$) was purchased from Aldrich and was dried under low pressure and at 120°C. Diisopropyl ethylamine (DIPEA) was purchased from Aldrich and used directly. Amino alcohols **4**-**9** were purchased from Aldrich Co. and amino alcohol **10** was prepared according to the literature methods.[1] Aldehydes were obtained from commercial sources and were distilled prior to use except 4-nitrobenzaldehyde which was used as received. When needed, purification of reaction products was carried out by flash chromatography using silica gel 60. ^{1}H NMR spectra were recorded on a Bruker AVANCE 500MHz or on a Varian GEMINI 200MHz spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; integration; coupling constant(s) in Hz. Analytical high performance liquid chromatography (HPLC) with chiral stationary phase was performed on

[1] S. Yao, J.-C. Meng, G. Siuzdak, and M. G. Finn, *J. Org. Chem.* **2003**, *68*, 2540.

Waters 600E and Hewlett Packard series 1050 chromatographs, equipped with a diode array UV detector, using Daicel Chiralpak AD, AS, IA, OJ and Chiralcel OD columns.

General Procedure for the Henry reaction. Method A.

To a suspension of $Zn(OTf)_2$[2] (108.9 mg, 0.3 mmol) in CH_3NO_2 (1 ml) was added diisopropylethylamine (DIPEA) (54 µL, 0.3 mmol) and the resulting yellow slurry stirred for 1h at room temperature. (1S,2R)-N-Methylephedrine ((+)-NME) (80.6 mg, 0.45 mmol) was then added and the mixture stirred for an additional 2h at room temperature. After cooling the mixture to —20°C, the corresponding aldehyde (net, 1 mmol) was added by syringe and the mixture stirred at that temperature, or otherwise stated temperature, for 16-18 h. The reaction was quenched with aqueous sat. NH_4Cl (1 mL), extracted with Et_2O (3 x 5 mL) and the combined organic layer washed with HCl 12 N (2 x 1 mL) and saturated NH_4Cl (1 x 1 mL). The organic layer was dried with $MgSO_4$ and the solvent evaporated. From the crude product, (+)-NME could be recovered as described below. When required, the nitroaldol adduct was purified by column chromatography.

General Procedure for the Henry reaction. Method B.

To a suspension of $Zn(OTf)_2$ (363.6 mg, 1mmol) in CH_3NO_2 (1 ml) was added diisopropylethylamine (DIPEA) (180 µL, 1mmol) and the resulting yellow slurry stirred for 1h at room temperature. (1S,2R)-N-Methylephedrine (268.9 mg, 1.5 mmol) was then added and the mixture stirred for an additional 2 h at room temperature. After addition of CH_2Cl_2 (1 mL), the reaction media was cooled to the stated temperature, and the aldehyde (net, 1 mmol) was added via syringe. The mixture was stirred at the same temperature for 16-18 h and then the same work-up as above provided the corresponding nitroaldol product.

[2] Replacing $Zn(OTf)_2$ by other salts such as $Mg(OTf)_2$, $Ba(OTf)_2$, and $Cu(OTf)_2$ led to racemic products.

Recovery of the aminoalcohol ligand

To the aqueous phase cooled in an ice bath was added drop-wise a solution of NaOH (20% w/v) until pH≥10 and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The organic layer was dried over $MgSO_4$ and evaporated at low pressure to afford (1S,2R)-N-methylephedrine chemically and optically pure in yields higher than 95%.

General Procedure for the preparation of racemic nitroaldols.

The general procedure A was followed using N,N-dimethyl ethanolamine instead of (1S,2R)-N-methylephedrine.

Assessment of the absolute configuration of adducts

The absolute configuration of adducts **3a,3d-k** was assigned by comparison of the measured optical rotations with literature data. The assignment for compounds **3b,c** was made by analogy and is supported by the consistent order of elution during chiral stationary phase HPLC. See the characterization data below for pertinent information.

Determination of non-linear effects

Four flasks, designated A-D, were charged with the following amounts of (+)-NME and (-)-NME.

A: 60 mg of (+)-NME and 40mg of (-)-NME (20% ee)
B: 70 mg of (+)-NME and 30mg of (-)-NME (40% ee)
C: 80 mg of (+)-NME and 20mg of (-)-NME (60% ee)
D: 90 mg of (+)-NME and 10mg of (-)-NME (80% ee)

The resulting mixtures of solids were dissolved in CH_2Cl_2 and then evaporated under reduced pressure. The resulting solids were dried under low pressure before taking the amount needed for reaction. The corresponding reactions were carried out according to the general procedure .The results are shown in Figure 1S.

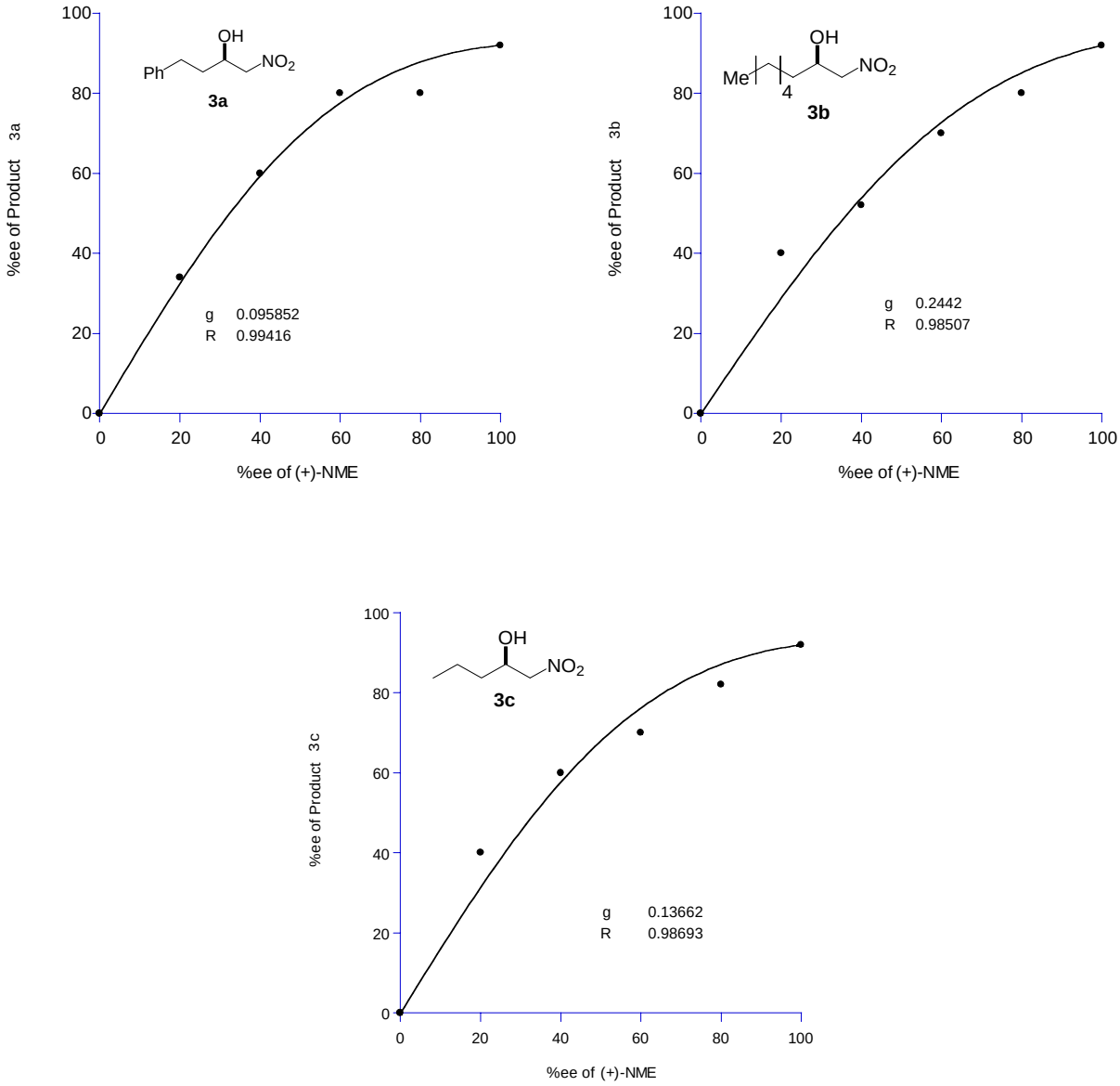
Assuming a two ligand model in a statistical distribution of ligands, curve fitting was calculated according to the following equation[3]:

$$ee_{prod} = ee_0 ee_{cat} \frac{2}{1 + g + (1 + g) ee_{cat}^{\ 2}}$$

where $g = k_{RS}/k_{RR}$
ee_{prod} = ee of the product obtained
ee_0 = ee of the product obtained with 100%ee ligand
ee_{cat}= ee of the ligand

[3] a)Mathematical correlation adapted from: C. Girard and H. B. Kagan, *Angew. Chem. Int. Ed.* **1998**, *37*, 2922-2959. b) D. Guillaneux, S. Zhao, O. Samuel, D. Rainford and H. B. Kagan, *J. Am. Chem. Soc.* **1994**, *116*, 9430-9439.

Figure 1S[4]. Computed curve fitting with two ligand model. Product ee vs. ligand ee in the Henry reaction of nitromethane with hydrocinnamaldehyde,heptanal, and butyraldehyde respectively, catalyzed by the $Zn(OTf)_2$:DIPEA:(+)-NME system.



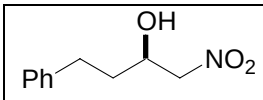
%ee (+)- NME	%ee Product,**3a**	%ee Product,**3b**	%ee Product,**3c**
0	0	0	0
20	34	40	40
40	60	52	60
60	80	70	70
80	80	80	82
100	90	92	92

[4] Graph obtained with Kaleidagraph for Windows, where R = Square Regression

Table 1S. Conversion dependence of Enantiomeric Purity[a]

Product	Load of cat	Time(min)	Conv, %[c]	e.e.%[d]
3a	30%	5	51	57
	30%	30	83	58
	30%	300	88	62
	30%	960	≥99	60
3b[b]	30%	1	37	72
	30%	5	55	72
	30%	30	80	70
	30%	960	≥99	70
3c	30%	1	23	63
	30%	5	50	66
	30%	30	74	66
	30%	300	80	62
	30%	960	90	60
	80%	960	91	65
	100%	960	92	63

[a] Reactions carried out with 40% ee of (+)- NME at 1 mmol scale in 1 mL of dry nitromethane with the corresponding aldehyde at −20°C, otherwise stated. [b] Reactions carried out with 60% ee of (+)-NME [c] Determined by ^{1}H-NMR (200MHz) after the indicated time. For product **3c** chemical yield instead of conversion is given. [d]Determined by HPLC; For **3a**: [Chiralpak IA 87/13 (hexane:propan-2-ol) flow:0.8ml/min]; For **3b** and **3c**: [Chiralpak IA 98/2 (hexane:propan-2-ol) flow:0.8ml/min]

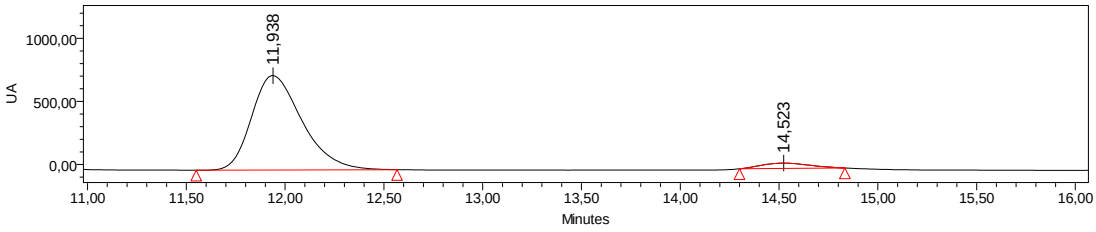


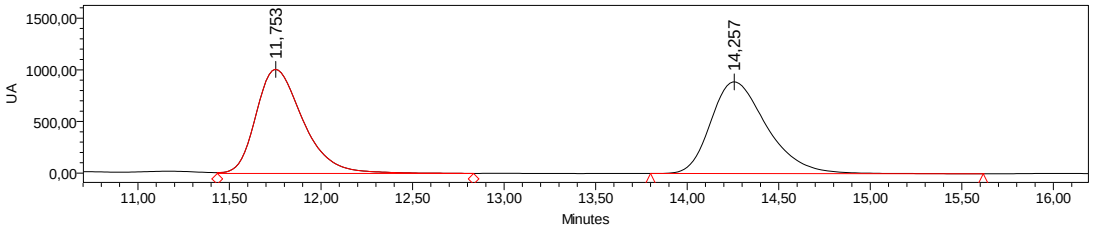
3a **(*R*)-1-Nitro-4-phenylbutan-2-ol.** The general procedure was followed. Yield 90%. Enantiomeric ratio (95:5) determined by HPLC analysis (Chiralpak IA 87:13 hex:^{i}PrOH, 0.8ml/min; (R) t_r, 12min; (S) t_r, 14.5min. $[\alpha]_D^{25}$ = +13.3 (c= 1, CH_2Cl_2) [Lit[5] +15.02,(c=1.33, CH_2Cl_2), 90%e.e.)].

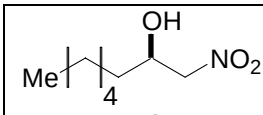
Processed Channel Descr.: @210nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	@210nm	11,938	13272046	94,80	749581
2	@210nm	14,523	728397	5,20	42838

^{1}H NMR (200 MHz, $CDCl_3$) 7.46-7.13 (m, 5H, Ar**H**), 4.44-5.36 (m, 2H, C**H**$_2$NO$_2$), 4.35-4.25 (m, 1H, C**H**OH), 2.97-2.63 (m, 2H, C**H**$_2$Ph), 2.36-2.05 (b, 1H, OH), 1.98-1.73 (m, 2H, C**H**$_2$CH$_2$Ph)





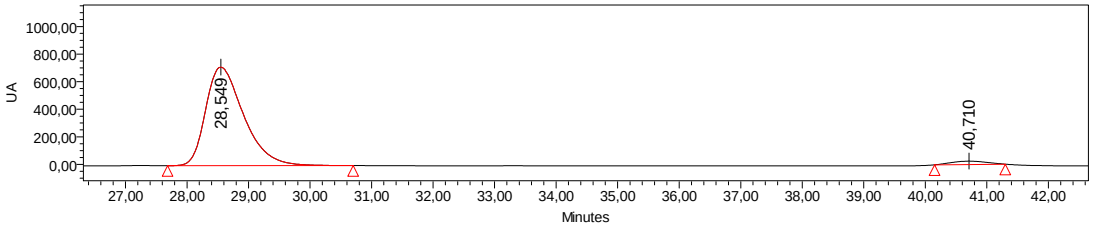


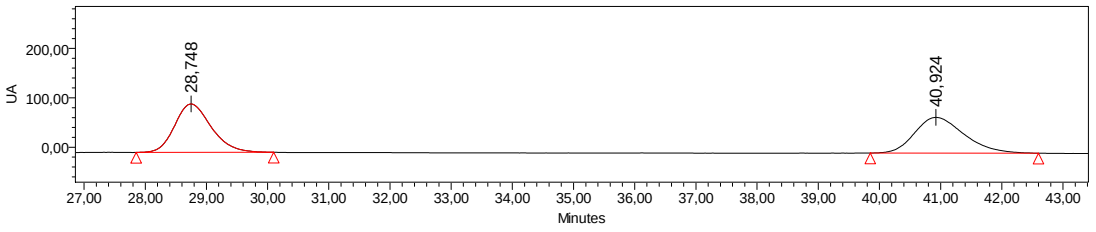
3b **(*R*)-1-nitrooctan-2-ol.** The general procedure was followed. Yield 83%. Enantiomeric ratio (97:3) determined by HPLC analysis (Chiralpak IA 98:2 hex:^{i}PrOH, 0.8ml/min; (R) t_r, 28min; (S) t_r, 40min. $[\alpha]_D^{25}$ = -12.3 (c= 1.2, CH_2Cl_2).

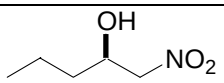
Processed Channel Descr.: @210nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	@210nm	28,549	30589875	96,95	715089
2	@210nm	40,710	961178	3,05	24243

^{1}H NMR (200 MHz, $CDCl_3$) 4.48-4.36 (m, 2H, C**H**$_2$NO$_2$, 4.35-4.26 (m, 1H, C**H**OH), 2.18-1.74 (m, 2H, CH$_2$C**H**$_2$CHOH), 1.65-1.10 (m, 9H, alkyl-**H** and OH), 0.86 (t, 3H, *J* = 6.5 Hz, C**H**$_3$)





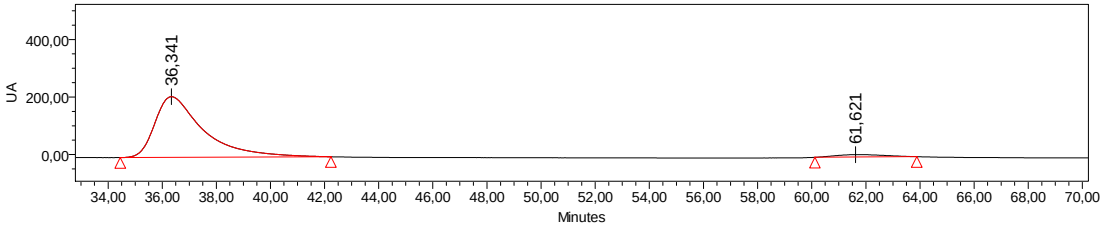


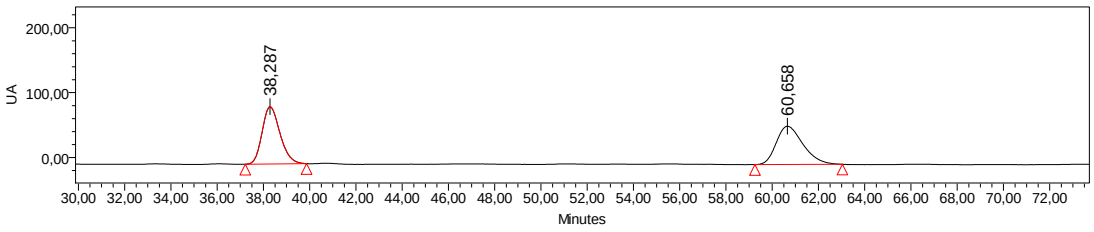
3c **(*R*)-1-nitropentan-2-ol.** The general procedure was followed. Yield 92%. Enantiomeric ratio (96:4) determined by HPLC analysis (Chiralpak IA 98:2 hex:^{i}PrOH, 0.8ml/min; (R) t_r, 36min; (S) t_r, 61min $[\alpha]_D^{25}$ = -18.3 (c= 2.3, CH_2Cl_2).

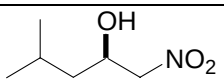
Processed Channel Descr.: @210nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	@210nm	36,341	26201429	96,12	211406
2	@210nm	61,621	1058328	3,88	8449

^{1}H NMR (200 MHz, $CDCl_3$) 4.51-4.36 (m, 2H, C**H**$_2$NO$_2$), 4.36-4.29 (m, 1H, C**H**OH), 2.98-2.68 (b, 1H, OH), 1.67-1.25 (m, 4H, alkyl-**H**), 0.97 (t, 3H, *J*= 6.8 Hz, C**H**$_3$).





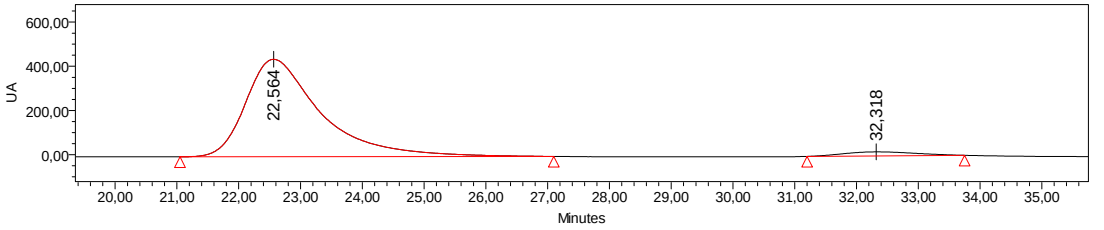


3d **(*R*)-4-Methyl-1-nitropentan-2-ol.** The general procedure was followed. Yield 75%. Enantiomeric ratio (96:4) determined by HPLC analysis[5] (Chiralcel OJ 98:2 hex:^{i}PrOH, 0.6ml/min; (R) t_r, 22.5min; (S) t_r, 32min. $[\alpha]_D^{25}$ = +2.4 (c= 1.2, CH_2Cl_2) [Lit[5] +2.6,(c=3.28, CH_2Cl_2), 92%e.e.)]

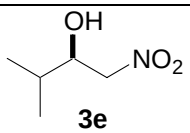
Processed Channel Descr.: @210nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	@210nm	22,564	37036829	96,19	440966
2	@210nm	32,318	1465099	3,81	18362

^{1}H NMR (200 MHz, $CDCl_3$) 4.49-4.26 (m, 3H, C**H**$_2$NO$_2$ and C**H**OH), 2.63-2.42 (b, 1H, OH), 1.96-1.68 (m, 1H, alkyl-**H**), 1.61-1.36 (m, 1H, alkyl-**H**), 1.32-1.10 (m, 1H, alkyl-**H**), 1.04-0.81 (apparent dd, 6H, *J*= 6.6, 2.8 Hz, CH_3).



[5] D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw, C. W. Downey, *J. Am. Chem. Soc.* **2003**, *125*, 12692-12693.

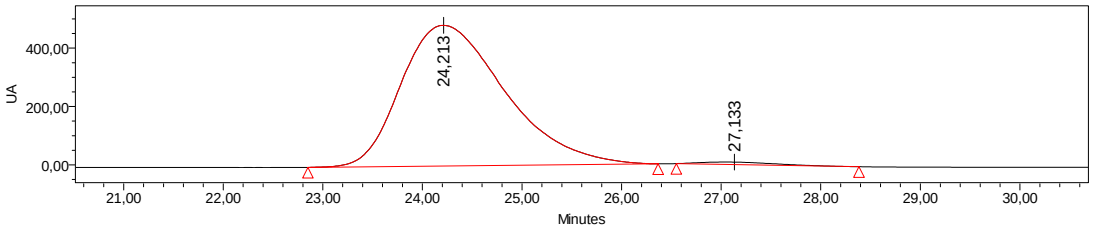


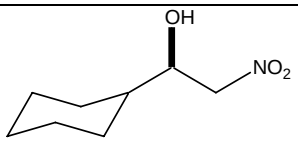
3e **(*R*)-3-Methyl-1-Nitrobutan-2-ol.** The general procedure was followed. Yield 68%. Enantiomeric ratio (99:1) determined by HPLC analysis[5] (Chiralcel OD 98:2 hex:^{i}PrOH, 0.6ml/min; (R) t_r, 25.5min; (S) t_r, 27min. $[\alpha]_D^{25}$ = -26.9 (c= 1, $CHCl_3$) [Lit[5] -29.2,(c=1.84, $CHCl_3$), 94%e.e.)][1]

^{1}H NMR (200 MHz, $CDCl_3$) 4.49-4.31 (m, 2H, C**H**$_2$NO$_2$), 4.17-4.05 (m, 1H, C**H**OH), 1.94-1.67(m, 1H, C**H**(CH$_3$)$_2$), 1.06-0.91(apparent dd, 6H, *J*= 6.8, 2.8 Hz, CH$_3$).

Processed Channel Descr.: @210nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	@210nm	24,213	34936417	98,78	482073
2	@210nm	27,133	432422	1,22	8522



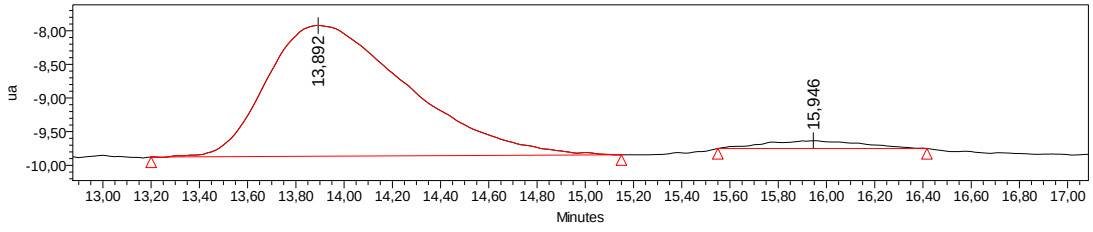


3f **(R)-1-cyclohexyl-2-nitroethanol.** The general procedure was followed. Yield 72%. Enantiomeric ratio (96:4) determined by HPLC analysis[6] (Chiralcel OD 97:3 hex:^{i}PrOH, 1ml/min; (R) t_r, 14min; (S) t_r, 16min. $[\alpha]_D^{25}$ = -20.3 (c= 1.2, $CHCl_3$) [Lit[5] -21.6,(c=1.33, $CHCl_3$), 93%e.e.)]

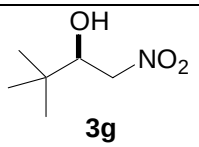
^{1}H NMR (200 MHz, $CDCl_3$) 4.58-4.28 (m, 2H, C**H**$_2$NO$_2$), 4.24-3.99 (m, 1H, C**H**OH), 2.36-2.06 (b, 1H, OH), 1.96-1.57 (m, 5H, cyclohexyl-**H**), 1.57-1.37 (m, 1H, cyclohexyl-**H**), 1.36-0.92 (m, 5H, cyclohexyl-**H**).

Processed Channel Descr.: @254nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	@254nm	13,892	79091	96,07	1944
2	@254nm	15,946	3239	3,93	115



[6] B. M. Trost, V. S. C. Yeh, *Angew. Chem.* **2002**, *114*, 889-891; *Angew. Chem. Int. Ed.* **2002**, *41*, 861-863.

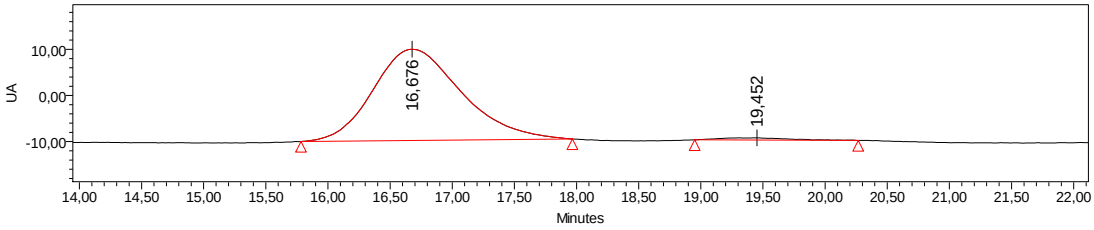


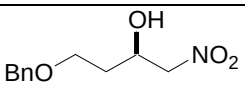
3g **(*R*)-3,3-Dimethyl-1-Nitrobutan-2-ol.** The general procedure was followed. Yield 71%. Enantiomeric ratio (98:2) determined by HPLC analysis[5] (Chiralcel OD 98:2 hex:^{i}PrOH, 0.8ml/min; (R) t_r, 16.5min; (S) t_r, 19min. $[\alpha]_D^{25}$ = -36.8 (c= 1, CH_2Cl_2) [Lit[5] -35.9,(c=1.01, CH_2Cl_2), 94%e.e.)]

Processed Channel Descr.: @210nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	@210nm	16,676	976524	98,12	19813
2	@210nm	19,452	18673	1,88	467

^{1}H NMR (200 MHz, $CDCl_3$) 4.58-4.47 (dd, 1H, *J*= 12.8, 2.27 Hz, C**H**$_2$NO$_2$), 4.43-4.28 (dd, 1H, *J*= 12.9, 9.8 Hz, C**H**$_2$NO$_2$), 4.07-3.98 (dd, 1H, *J*= 9.8, 2.3 Hz, C**H**OH), 2.88-2.69 (b, 1H, OH), 0.97 (s, 9H, C(C**H**$_3$)$_3$).



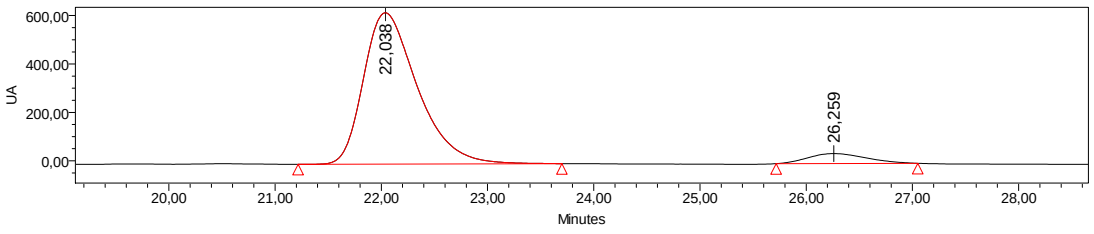


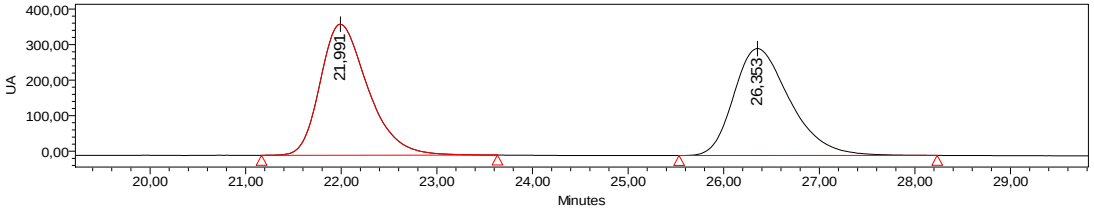
3h **(R)-4-(benzyloxy)-1-nitrobutan-2-ol.** The general procedure was followed. Yield 82%. Enantiomeric ratio (93.5:6.5) determined by HPLC analysis (Chiralcel OD 95:5 hex:^{i}PrOH, 1ml/min; (R) t_r, 22min; (S) t_r, 26min. $[\alpha]_D^{25}$ = -1.4 (c= 0.59, CH_2Cl_2) [Lit[6] (S) enant. +0.52,(c=0.59, CH_2Cl_2), 86%e.e.)]

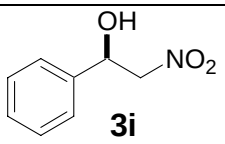
Processed Channel Descr.: @210nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	@210nm	22,038	21964986	93,42	624904
2	@210nm	26,259	1546642	6,58	40947

^{1}H NMR (200 MHz, $CDCl_3$) 7.42-7.26 (m, 5H, ArH), 4.52 (s, 2H, ArC**H**$_2$O), 4.56-4.49 (m, 1H, C**H**OH), 4.44 (dd, *J*= 7.1, 1.8 Hz, 2H, C**H**$_2$NO$_2$), 3.75-3.66 (m, 2H, C**H**$_2$OCH$_2$Ar), 2.45-1.96 (b, 1H, O**H**), 1.92-1.76 (m, 2H, C**H**$_2$CHOH)





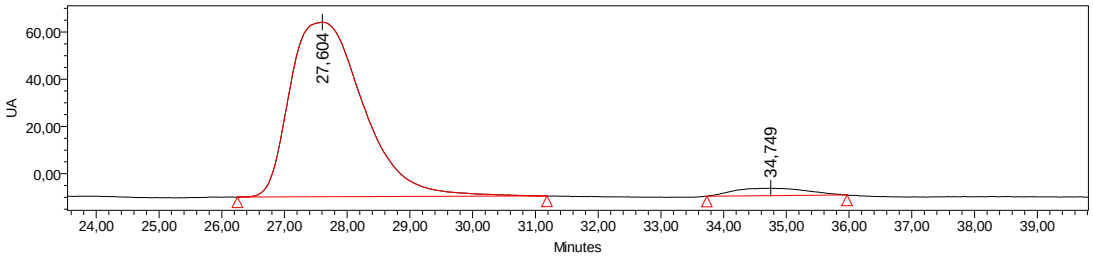


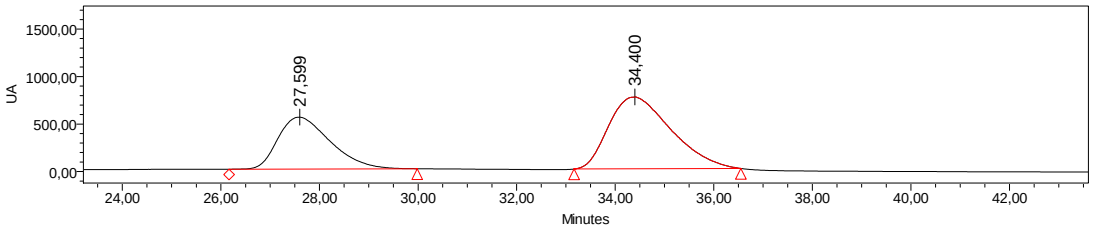
3i **(*R*)-1-Phenyl-2-nitroethanol.** The general procedure was followed. Yield 85%. Enantiomeric ratio (96:4) determined by HPLC analysis (Chiralcel OD 90:10 hex:^{i}PrOH, 0.5ml/min; (R) t_r, 28min; (S) t_r, 35min. $[\alpha]_D^{25}$ = -39.0 (c= 1, CH_2Cl_2) [Lit[5] -41.6,(c=1.03, CH_2Cl_2), 94%e.e.)]

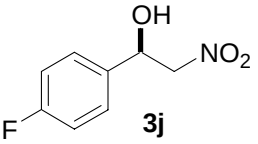
^{1}H NMR (200 MHz, $CDCl_3$) 7.47-7.34 (m, 5H, Ar**H**), 5.56-5.38 (m, 1H, C**H**OH), 4.71-4.45 (m, 2H, C**H**$_2$NO$_2$), 2.50 (b, 1H, OH).

Processed Channel Descr.: @210nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	@210nm	27,604	6006619	95,94	73921
2	@210nm	34,749	254068	4,06	3145





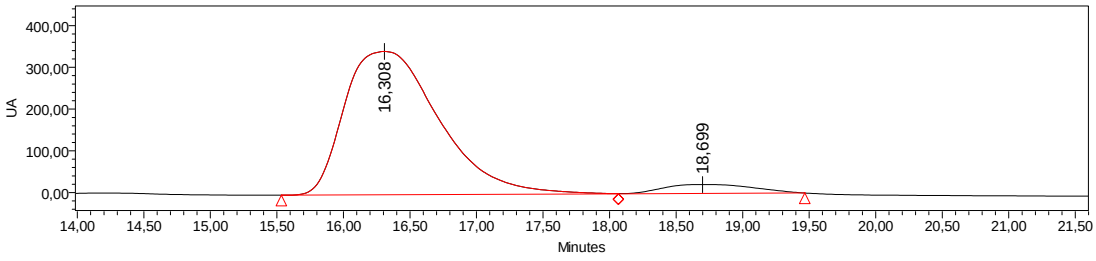


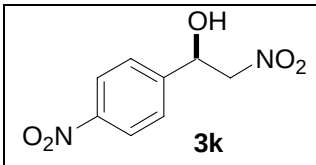
3j **(*R*)-1-4-(Fluorophenyl)-2-nitroethanol.** The general procedure was followed. Yield 70%. Enantiomeric ratio (94.5:5.5) determined by HPLC analysis[5] (Chiralcel OD 85:15 hex:^{i}PrOH, 0.5ml/min; (R) t_r, 17min; (S) t_r, 19.5min. $[\alpha]_D^{25}$ = -40.1 (c= 1.2, CH_2Cl_2) [Lit[5] -44.8,(c=1.05, CH_2Cl_2), 92%e.e.)]

^{1}H NMR (200 MHz, $CDCl_3$) 7.55-7.30 (m, 2H, ArH), 7.21-7.00 (m, 2H, ArH), 5.53-5.39 (dd, 1H, *J* = 8.8, 3.1 Hz, CH_2OH), 4.69-4.40 (m, 2H, CH_2NO_2), 3.46-3.16 (b, 1H, OH).

Processed Channel Descr.: @210nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	@210nm	16,308	16948664	94,41	343315
2	@210nm	18,699	1004084	5,59	21370





3k

Processed Channel Descr.: @210nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	@210nm	28,264	11790166	92,03	171640
2	@210nm	35,927	1021311	7,97	13796

(*R*)-2-Nitro-1-(4-Nitrophenyl) ethanol. The general procedure was followed. Yield 77%. Enantiomeric ratio (92:8) determined by HPLC analysis (Chiralcel OD 85:15 hex:^{i}PrOH, 0.5ml/min; (R) t_r, 32.5min; (S) t_r, 41min. $[\alpha]_D^{25}$ = -38.4 (c= 1.3, CH_2Cl_2) [Lit[5] -31.6,(c=1.05, CH_2Cl_2), 78%e.e.)][5]

^{1}H NMR (200 MHz, $CDCl_3$) 8.34-8.18 (m, 2H, ArH), 7.70-7.53 (m, 2H, ArH), 5.68-5.53 (dd, 1H, *J*= 7.1, 4.7 Hz CHOH), 4.65-4.50 (m, 2H, CH_2NO_2), 3.32-3.10 (b, 1H, OH).