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Synthesis of chiral salan ligands with bulky substituents and their application in Cu-catalyzed asymmetric Henry reaction

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ABSTRACT

Several new chiral *N,N'*-dimethylated salan ligands with bulky substituents were synthesized and their in-situ generated Cu(II) complexes were evaluated in the asymmetric Henry reaction. Substituents on the aryloxide moieties of these ligands were found to show remarkable effect on the enantioselectivity. Cu(II) complex generated from the ligand with 1,1-diphenylethyl groups at the *ortho*-position of the aryloxide moieties and $Cu(OAc)_2 \cdot H_2O$ was found to show good catalytic performance, giving the 2-nitro-1-phenylethanol product in 85% yield with 94% ee in the presence of TEA in THF at -20 °C. The catalyst systems were examined with different aldehydes and the corresponding products were obtained in good yields (up to 94%) with 85% to 95% ee in the presence or absence of TEA. Diastereoselective reactions using nitroethane as the nucleophile afford *syn*-β-nitroalcohols in good yields (48%-66%) with good dr (up to 11.5:1 *syn*/*anti*) and high ee values (92%-96%).

1. Introduction

Henry (nitro-aldol) reaction is one of the most renowned methodologies for carbon-carbon bond formation in organic synthesis. The resultant β-hydroxy nitro compounds are valuable starting materials for further synthesis. [1] Since the first enantioselective Henry reaction was reported by Shibasaki in 1992,[2] significant research efforts have been made and various efficient chiral catalyst systems for the reaction have been developed. Among the enormous reports, the copper catalyzed Henry reaction have received much attention since copper is cheap and of low toxicity, and its complexs show good tolerance for air and moisture [3].

The design and development of highly efficient and selective ligands play a pivotal role in metal-catalyzed asymmetric reactions. Compared with salen ligands, the salan (tetrahydrosalen) analogues are structurally more flexible and with increased N basicity. In addition, the salan ligands bind to a metal atom in a non-planar arrangement, leading to their metal complexes exert evident asymmetric feature. [4] So far, great efforts have been devoted toward the development of asymmetric Henry reaction catalyzed by salan-copper catalyst systems and the salan-copper complexes bearing ligands with 1,2-diaminobicyclo[2.2.2]octane, [5] 1,2-diamino-1,2-diphenyl- ethane, [6] 1,2-diaminocyclohexane, [7] 2,5-diamino-bicyclo[2.2.2]octane [8] and C-Pyrrolidin-2-yl-methylamine [9] skeletons have been reported to show moderate to strong asymmetric inductivity for producing β-hydroxy nitro compounds with good to excellent ee values. Very few other metal complexes with salan ligands were reported for the asymmetric Henry reaction [10].

Chiral *N*-Me substituted salan ligands have been employed in catalysts for polymerization of α-olefins, ring-opening polymerization of lactide and copolymerization of CO_2 with propylene oxide, which exhibit strong stereochemistry control ability. [11] It has been reported that catalysts with the 1,2-diaminocyclohexane skeleton containing salan ligands exhibit superior catalytic performances for the nitro-aldol reaction in comparison to catalysts bearing related salalen and salalan ligands, and the *N,N'*-substituents in the salan ligands play a crucial role on the enantioselectivity. [12] For catalysts bearing salen ligands, substituents on the salicylidene moieties were also reported to show remarkable effect on the enantioselectivity of products in nitro-aldol reactions. (Salen)Cr(III)Cl complexes with bulky substituents in the 3,3′-positions of the salicylidene moieties lead to products with higher ee values [13].

So far, little work have been focused on the steric effect of the substitutes on the aryloxide moieties of the salan ligands in the catalysts for Henry reaction. We have synthesized a number of new chiral *N,N'*-dimethylated salan ligands with bulky substituents at the *ortho*-position of the aryloxide moieties, examined the catalytic performance of their in-situ formed Cu(II) complexes in Henry

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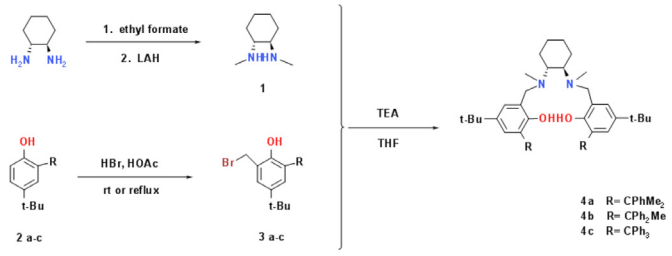


Scheme 1. Synthetic routes for ligands **4a-c**.

reaction and found that catalysts formed from the salan ligands with moderately bulky substituents show the best enantioselectivity. Herein we report the synthesis of these *N,N'*-dimethylated salan ligands and their application in the Cu(II)-catalyzed asymmetric Henry reaction.

2. Results and discussion

2.1. Preparation of chiral ligands

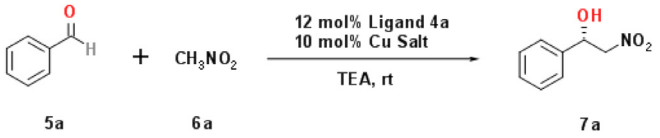
In principle, the *N*-Me-substituted salan ligands can be prepared through several synthetic routes. One is through the condensation between a diamine and 2 equiv of a salicylaldehyde first, followed by reduction of the formed imine functionalities with $NaBH_4$ (or $LiAlH_4$) to yield the [4H]salen ligands, then further condensation with formaldehyde and reduction to obtain the *N*-Me-substituted ligands. This synthetic route is a convenient method when the salicylaldehyde material is commercially available. Another effective route for the synthesis of this type of ligands is the Mannich condensation between formaldehyde, a *N,N'*-dimethyldiamine and a phenol material. This method was reported to give lower yields with 1,2-*N,N'*-(dimethyl)diamino-cyclohexane [14] than with *N,N'*-dimethylethylenediamine as starting material. [15] The third method for preparing the *N*-Me-substituted salan ligands is by the reaction between a *N,N'*-dimethyldiamine and an *ortho*-bromomethylphenol which have been applied in the synthesis of C_1-symmetric [ONNO']-type salan ligands, [16] salalen ligands, [17] [ONSO]-type ligands [18] and C_2-symmetric [OSSO]-type ligands. [19] We found that the first two synthetic routes don't work very well for preparing the *N,N'*-dimethylated salan ligands with bulky substituents and therefore we use the third method to synthesize the new chiral salan ligands **4a, 4b** and **4c** as shown in Scheme 1. The (R,R)-*N,N'*-Dimethyl-1,2-cyclohexanediamine **1** was prepared as a colourless crystalline solid in high yield by a routine methodology involving the transesterification of ethyl formate with (R,R)-cyclohexanediamine followed by reduction of the bis(amide) intermediate with $LiAlH_4$ in THF. The bulky subsitituents were introduced to the *ortho*-position of the phenols via alkylation of 4-*tert*-butylphenol with corresponding alkenes or trityl chloride.

The 2-(bromomethyl)-4-*tert*-butyl-6-substituted-phenols **3a-c** were synthesized by bromomethylation of the corresponding phenols **2a-c** using saturated HBr (in HOAc) and paraformaldehyde. Finally, reaction of 2 equiv of bromomethyl phenols **3a-c** with cyclohexanediamine **1** in the presence of triethylamine gave the chiral salan ligands **4a-c** in high yields. All three ligands were characterized by ^1H, ^{13}C NMR and HRMS. These new ligands were found to be stable in air for months.

2.2. Enantioselective Henry reaction

With these new chiral salan ligands, Cu(II)-catalyzed asymmetric Henry reactions were investigated to evaluate their ability of asymmetric induction. In a preliminary study, nirtroaldol reactions of benzaldehyde using the catalyst in-situ formed from ligand **4a** and $Cu(OAc)_2{\cdot}H_2O$ were examined and the results are listed in Table 1. From these results, evident solvent effect on the enantioselectivity of the **4a**/$Cu(OAc)_2{\cdot}H_2O$ catalyzed nirtroaldol reactions of benzaldehyde was observed (entries 1–4 in Table 1). Among the screened solvents, THF was proved to be the most suitable solvent for this reaction with an enantio-selectivity of 77% and a yield of 80%. It was found that reactions in ethanol and DCM give high yields but low ee values. Moderate values of enantiomeric excess (49%) and yield (60%) were acquired with toluene as the solvent. Alcohols [5,6a,6d,8] and THF [6b,6c,6e,7] have been reported to be suitable solvents for similar catalytic reactions using chiral salan ligands.

Table 1
Results of nirtroaldol reactions of benzaldehyde catalyzed by **4a**/$Cu(OAc)_2{\cdot}H_2O$[a].



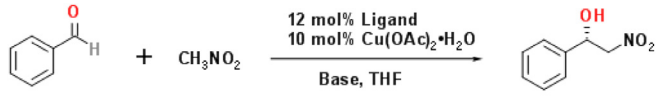
Entry	Slovent	Cu salt	Time/h	Yield[b]/%	ee[c]/%
1	EtOH	$Cu(OAc)_2{\cdot}H_2O$	48	95	28
2	DCM	$Cu(OAc)_2{\cdot}H_2O$	48	74	22
3	toluene	$Cu(OAc)_2{\cdot}H_2O$	48	60	49
4	THF	$Cu(OAc)_2{\cdot}H_2O$	48	80	77
5	THF	$CuCl_2{\cdot}2H_2O$	48	75	74
6	THF	$CuSO_4{\cdot}5H_2O$	72	trace	nd
7	THF	–	48	trace	nd
8[d]	THF	–	48	trace	nd

[a] Reactions were carried out at room temperature on 0.5 mmol scale with 0.27 ml of nitromethane in the presence of 20 mol% TEA in 2 ml of solvent.
[b] Isolated yield.
[c] Determined by HPLC with a chiral column.
[d] Reaction was carried out without ligand 4a.

A number of copper salts were also evaluated in combination with **4a** in THF. The best ee value of 77% from the **4a**/$Cu(OAc)_2{\cdot}H_2O$ system and a high ee value of 74% from the **4a**/$CuCl_2{\cdot}2H_2O$ system were obtained with high yields, while only trace of product was observed from the **4a**/$CuSO_4{\cdot}5H_2O$ system even the reaction was kept for long time. When reactions were carried out without any Cu salt (entry 7 in Table 1), or without both the ligand and Cu salt (entry 8 in Table 1), no product was observed.

Considering that the deprotonation of nitromethane is a rate determining step in Henry reaction, the effect of the base was examined. The reaction with TEA as the base was found to give the product in the highest yield with the highest ee value, and the reaction with *N,N*-Diisopropylethylamine (DIPEA) as the base formed the product in slightly lower yield and ee value (entries 1 and 2 in Table 2). Na_2CO_3 was also found to be suitable base for the reaction although the product was obtained in relatively low yield (entry 3 in Table 2). Decreasing the amount of TEA to 10 mol % leads to a slight increase in the ee value and a mild decrease in the product yield (comparing entries 1 and 4 in Table 2), while decreasing the loadings of catalyst and TEA to 50% lead to remarkable decrease in the product yield (comparing entries 1 and 5 in Table 2). A pre-formed 4a-Cu complex grnerated from reaction of ligand 4a and $Cu(OAc)_2{\cdot}H_2O$ in 1:1 ratio in ethanol was also examined as catalyst, and similar yields and enantioselectivities to those observed in the *in-situ* generated catalyst system were achieved (compring entries 4 and 6 in Table 2). The reaction in the absence of any base led to almost no product (entry 7 in Table 2). We also evaluated the performance of ligands **4a-c** under different conditions. It was found that the **4b**/$Cu(OAc)_2{\cdot}H_2O$ catalyst system afford the product in the highest yield and ee value (entry 8 in Table 2). The high product yield from the **4b**/$Cu(OAc)_2{\cdot}H_2O$ catalyst system may be due to the integrated

Table 2
Results of nirtroaldol reactions of benzaldehyde catalyzed by ligands **4a-c**/$Cu(OAc)_2{\cdot}H_2O$ systems in the presence of different bases[a].

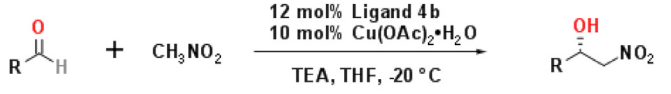


5a 6a 7a

Entry	Ligand	Base	Time/h	Yield[b] /%	ee[c]/%
1	**4a**	20mol% TEA	48	80	77
2	**4a**	20mol% DIPEA	48	73	74
3	**4a**	20mol% Na_2CO_3	48	40	75
4	**4a**	10mol% TEA	48	74	82
5[d]	**4a**	10mol% TEA	48	53	78
6[e]	**4a-Cu**	10mol% TEA	48	73	82
7	**4a**	–	48	trace	nd
8	**4b**	10mol% TEA	48	88	85
9	**4c**	10mol% TEA	48	82	62
10[f]	**4b**	10mol% TEA	96	90	90
11[g]	**4b**	10mol% TEA	96	84	94
12[h]	**4b**	10mol% TEA	96	trace	nd

[a] Reactions were carried out on 0.5 mmol scale with 0.27 ml of nitromethane in 2 ml of THF.
[b] Isolated yield.
[c] Determined by HPLC with a chiral column.
[d] 6 mol% 4a and 5 mol% $Cu(OAc)_2{\cdot}H_2O$ were used as catalysts.
[e] 10 mol% pre-formed 4a-Cu complex was used as catalyst
[f] The reaction was carried out at 0 °C.
[g] The reaction was carried out at -20 °C.
[h] The reaction was carried out at -40 °C.

Table 3
Results of nirtroaldol reactions of various aldehydes catalyzed by ligand **4b**/$Cu(OAc)_2{\cdot}H_2O$ system[a].



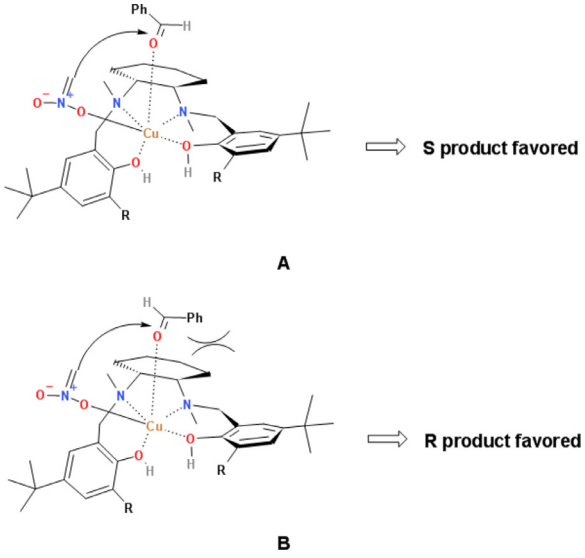
5a-5p 6a 7a-7p

Entry	Aldehyde	Product	Time/h	Yield[b] /%	ee[c]/%
1	C_6H_5CHO	7a	96	84	94
2	2-MeC_6H_4CHO	7b	96	62	91
3	3-MeC_6H_4CHO	7c	96	65	88
4	4-MeC_6H_4CHO	7d	96	56	92
5	2-$MeOC_6H_4CHO$	7e	96	95	90
6	3-$MeOC_6H_4CHO$	7f	96	81	95
7	4-$MeOC_6H_4CHO$	7g	96	55	91
8	2-ClC_6H_4CHO	7h	72	94	85
9	4-ClC_6H_4CHO	7i	72	63	93
10	2-BrC_6H_4CHO	7j	72	92	90
11	4-BrC_6H_4CHO	7k	72	74	90
12	2-$NO_2C_6H_4CHO$	7l	72	96	82
13	4-$NO_2C_6H_4CHO$	7m	72	84	75
14	1-Naphthaldehyde	7n	96	62	90
15	2-Naphthaldehyde	7o	96	80	88
16	*c*-$C_6H_{11}CHO$	7p	96	54	94

[a] Reactions were carried out on 0.5 mmol scale with 0.27 ml of nitromethane in 2 ml of THF.
[b] Isolated yield.
[c] Determined by HPLC with a chiral column, the absolute configuration was established as S by comparison retention time with literature data [20].

results of the electronic effect and steric effect of the ligands. The electron-withdrawing ability of 1,1-diphenylethyl and trityl groups are stronger than that of cumyl group, which can be identified by comparing the *OH* chemical shifts of the corresponding phenols **2a-c**. The catalytic activity of the **4b** and **4c** systems should thus be higher than that of the **4a** system, while the catalytic activity of the **4c** system is lower than the one of the **4b** system should be caused by the too bulky trityl groups in the ligand **4c**. The value of 85% ee is higher than the reported 78% ee for the same product obtained with a Cu complex bearing the 6,6′-(((1R,2R)-Cyclohexane-1,2-diylbis(methylazanediyl))bis(methylene))bis-(2,4-di-tert-butylphenol) ligand.[12] The enantio-selectivity was further improved to 90% ee and 94% ee when the reaction was carried out at 0 °C and -20 °C (entries 10 and 11 in Table 2) respectively.

Furthermore, enantio-selective nitroaldol reactions of various aldehydes with nitromethane were investigated with the **4b**/$Cu(OAc)_2{\cdot}H_2O$ catalyst system under the optimized conditions [10 mol% Cu catalyst, $Cu(OAc)_2{\cdot}H_2O$/ligand **4b** = 1 : 1.2, 10 mol% TEA in THF at -20 °C]. The results are summarized in Table 3. As expected, the benzaldehyde derivatives with an electron-withdrawing group were found to be more reactive than those with an electron-donating group. However, it seems difficult to find an unambiguous relationship between the enantio-selectivity of these reactions and the electronic effect of the substituent on these benzaldehyde derivatives although the strongly electron-withdrawing nitro group leads to obvious decrease in the enantioselectivity of the reactions of related benzaldehyde derivatives (entries 12 and 13 in Table 3). For a given substituent, the reactions of ortho-substituted benzaldehyde derivatives were found to result in higher yields than those of para-substituted benzaldehyde derivatives do. The naphthaldehydes were found to be suitable for the nitroaldol reaction, giving the desired products in moderate yields and high ee values (entries 14 and 15 in Table 3). In addition, aliphatic aldehyde was found to be good substrate, cyclohexanecarboxaldehyde underwent reaction with 52% yield and 94% ee (entry 16 in Table 3). Overall, the nitroaldol reactions of the selected benzaldehyde derivatives

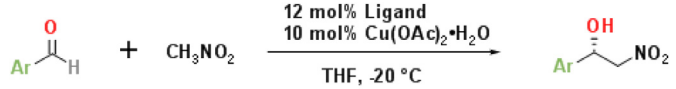


Scheme 2. Proposed transition state for the reaction of aldehyde with nitromethane catalyzed by salan ligands.

catalyzed by ligand **4b**/$Cu(OAc)_2{\cdot}H_2O$ system exhibit superior enantio-selectivity in comparison to the reported reactions catalyzed by a similar salan Cu complex bearing a 6,6′-(((1R,2R)-Cyclohexane-1,2-diylbis(methylazanediyl))bis(methylene))bis-(2,4-di-tert-butylphenol) ligand [12].

The asymmetric induction mechanism should be similar to Feng's tetrahydrosalen/$(CuOTf)_2C_7H_8$ catalyst system, leading to the products with S configuration. [6a] The proposed transition state A is more stable than that of the transition state B as the increased repulsion between the benzaldehyde and cyclohexyl skeleton in B, and the carbonyl of benzaldehyde in the ransition state A is more easily accessible to a nucleophilic group which leads to the S-configured β-nitro alcohols. than the state B (Scheme 2).

Table 4
Results of nirtroaldol reactions of nitrobenzaldehydes without any base[a].

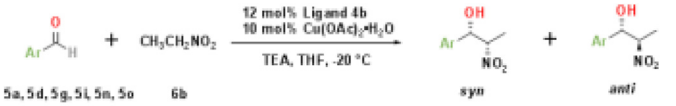


5l, 5m 6a 7l, 7m

Entry	Ligand	Aldehyde	Time/h	Yield[b] /%	ee[c] /%
1	**4a**	2-$NO_2C_6H_4CHO$	96	60	43
2	**4b**	2-$NO_2C_6H_4CHO$	96	74	88
3	**4c**	2-$NO_2C_6H_4CHO$	96	72	95
4	**4a**	4-$NO_2C_6H_4CHO$	96	40	65
5	**4b**	4-$NO_2C_6H_4CHO$	96	60	86
6	**4c**	4-$NO_2C_6H_4CHO$	96	68	90

[a] Reactions were carried out on 0.5 mmol scale with 0.27 ml of nitromethane in 2 ml of THF.
[b] Isolated yield.
[c] Determined by HPLC with a chiral column.

Table 5
Results of nirtroaldol reactions between arylaldehydes and prochiral nitroethane[a].



5a, 5d, 5g, 5i, 5n, 5o 6b 8a, 8d, 8g, 8i, 8n, 8o

Entry	Aldehyde	Product	Yield[b] /%	*syn*/*anti*	ee[c] /% (*syn*/*anti*)
1	C_6H_5CHO	8a	60	60/40	92/67
2	4-MeC_6H_4CHO	8d	48	61/39	95/73
3	4-$MeOC_6H_4CHO$	8g	50	67/33	95/60
4	4-ClC_6H_4CHO	8i	66	69/31	96/80
5	1-naphthaldehyde	8n	58	92/8	94/44
6	2- naphthaldehyde	8o	70	67/33	96/77

[a] Reactions were carried out on 0.5 mmol scale with 0.36 ml of nitroethane in 2 ml of THF and run for 96 h.
[b] Isolated yield.
[c] Determined by HPLC with a chiral column.

Due to the strong electron-withdrawing ability of the nitro group, 2-nitrobenzaldehyde and 4-nitrobenzaldehyde were found to show relatively high reactivity and undergo the nirtro-aldol reaction with nitromethane in the absence of any base. Reactions in the presence of $Cu(OAc)_2{\cdot}H_2O$ and a chiral ligand from **4a-c** were evaluated and the results are listed in Table 4. It was seen that the ee values for the products from the reactions in the absence of any base (entries 2 and 5 in Table 4) increase obviously compared to the ones from similar reactions in the presence of TEA (entries 12 and 13 in Table 3). Another interesting thing noticed from these reactions without any base is that the reaction in the presence of a bulkier ligand lead to a product with a higher ee value. The best results were obtained with reactions catalysed by ligand **4c**/$Cu(OAc)_2{\cdot}H_2O$ catalyst system (95% ee and 90% ee for products from 2-nitrobenzaldehyde and 4-nitrobenzaldehyde, respectively, entries 3 and 6 in Table 4). In addition, these ee values are relatively high in comparison to the data (90% ee and 76% ee for products from 2-nitrobenzaldehyde and 4-nitrobenzaldehyde, respectively) from similar reactions catalyzed by a Cu complex bearing a 6,6′-(((1R,2R)-Cyclohexane-1,2-diylbis(methyl-azanediyl)) bis(methylene))bis-(2,4-di-tert-butylphenol) ligand [12].

To further evaluate this catalytic system, diastereoselective Henry reactions using nitroethane as the nucleophile were also examed with aromatic aldehydes. (Table 5) Mixtures of *syn*- and *anti*-isomers with moderate yields (48%-66%) were obtained from these reactions. A remarkable increase in the diastereoselectivity of these reactions was observed with the variation in the starting material from benzaldehyde (*syn*/*anti* = 60/40) to 1-naphthylaldehyde (*syn*/*anti* = 92/8). Similar results were also noticed by Wan's group with a bis(sulfonamide)-diamine tetradentate/CuBr catalyst system.[21] The major *syn*-isomers formed from these reactions show high ee values (92%-96%), while the enantioselectivity of the minor anti-isomers were relatively low. The absolute configuration of major *syn*-isomers were determined to be (1S, 2S) by comparing the HPLC diagrams with literature data [20d,21,22].

3. Conclusion

A number of new chiral *N,N'*-dimethylated salan ligands with bulky substituents were synthesized, and a series of chiral β-nitro alcohols were obtained in high yields with good enantioselectivity (up to 95% ee) from nitro-aldol reactions of nitromethane with different aldehydes using Cu(II) complex generated in-situ with these chiral salan ligands. Substituents on the aryloxide moieties of these salan ligands were found to show remarkable effect on the enantioselectivity of nitro-aldol products. Cu(II) complex generated in-situ with the ligand with 1,1-diphenylethyl groups at the ortho-position of the aryloxide moieties was found to show good catalytic performance for the nitro-aldol reaction between benzaldehyde and nitromethane, giving the corresponding product in 85% yield and 94% enantiomeric excess. The presence of a suitable base was found necessary for the nitro-aldol reaction of most aldehyde starting materials, while 2-nitrobenzaldehyde and 4-nitrobenzaldehyde were observed to show relatively high reactivity and undergo the nirtro-aldol reaction in the absence of any base. In addition, syn-β-nitroalcohols with good dr (up to 11.5:1 syn/anti) and high ee values (92%-96%) were also achieved in mod-

erate yields (48%-66%) from the diastereoselective Henry reactions using nitroethane as the nucleophile.

4. Experimental section

4.1. General

Reagents and solvents were purchased commercially and used as received without further purification. ^{1}H and ^{13}C spectra were obtained by using a Bruker AVANCE-400 NMR spectrometer. Chemical shifts were reported in ppm using the solvent resonance as the internal standard ($CDCl_3$, δ = 7.26 ppm for ^{1}H NMR, δ = 77.16 ppm for ^{13}C NMR). Mass spectrometry analysis were recorded on a Thermo Q-Exactive Orbitrap mass spectrometer in ESI^+ mode. Enantiomeric excesses (ee) were determinded by HPLC analysis on a Chiralcel OD-H or Chiralcel AD-H column at 254 nm. The *syn/anti* ratios were calculated on the basis of ^{1}H NMR spectroscopic analysis.

4.2. Synthesis of ligands

4.2.1. (R,R)-N,N'-Dimethyl-cyclohexane-1,2-diamine (1)

The compound **1** was prepared in 80% yield from (R,R)-1,2-cyclohexanediamine according to a literature proceture [23] .

4.2.2. 4-(Tert-butyl)-2-(2-phenylpropan-2-yl)phenol (2a)

The compound **2a** was synthesized according to a literature procedure. [13] A mixture of 4-tert-butyl-phenol (7.51 g, 50 mmol), isopropenylbenzene (6.5 ml, 50 mmol) and $TsOH{\cdot}H_2O$ (0.095 g, 0.5 mmol) was stirred without solvent at 120 °C for 3 h. After the mixture was cooled down to the room temperature, the crude product was purified by column chromatography on a silica column with a hexane/EtOAc (v/v, 50/1) eluant to give **2a** as a colorless oil (9.18 g, 34.2 mmol. 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 7.48–6.65 (m, 8H, Ar*H*), 4.17 (br s, 1H, O*H*), 1.69 (s, 6H, C(CH_3)$_2$Ph), 1.35 (s, 9H, C(CH_3)$_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ 151.50, 148.64, 143.21, 134.59, 129.27, 127.02, 126.13, 124.85, 123.27, 117.20, 41.99, 34.50, 31.84, 29.75 ppm.

4.2.3. 4-(Tert-butyl)-2-(1,1-diphenylethyl)phenol (2b)

A solution of 4-tert-butyl-phenol (6.26 g, 41.7 mmol), 1,1-diphenylethylene (5.3 ml, 30 mmol) and anhydrous $FeCl_3$ (0.45 g, 2.8 mmol) in cyclohexane (80 ml) was stirred at 55 °C for 12 h. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on a silica column with a hexane/EtOAc (v/v, 50/1) eluant to give 2b as a white solid (5.06 g, 15.3 mmol. 51% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 7.34–6.72 (m, 13H, Ar*H*), 4.33 (br s, 1H, O*H*), 2.22 (s, 3H, C(CH_3)Ph$_2$), 1.17 (s, 9H, C(CH_3)$_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ 151.75, 146.67, 143.13, 133.81, 128.63, 128.40, 126.84, 126.66, 125.10, 117.27, 51.40, 34.31, 31.58, 28.99 ppm.

4.2.4. 4-(Tert-butyl)-2-(trityl)phenol (2c)

The compound **2c** was synthesized according to a literature procedure. [24] A mixture of 4-tert-butyl-phenol (6.46 g, 43 mmol), trityl chloride (6.69 g, 24 mmol) was stirred without solvent at 165 °C for 10 h under nitrogen atmosphere. The mixture was cooled down to room temperature, dissolved in diethyl ether and diluted with 2 M NaOH solution. The organic layer was separated and dried over anhydrous $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography on a silica column with a hexane/EtOAc (v/v, 50/1) eluant to give **2c** as a white solid (3.81 g, 9.7 mmol. 40% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 7.29–6.75 (m, 18H, Ar*H*), 4.32 (br s, 1H, O*H*), 1.15 (s, 9H, C(CH_3)$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ 152.16, 144.43, 142.79, 132.38, 131.13, 128.03, 128.00, 126.87, 125.56, 117.34, 63.02, 34.35, 31.58 ppm.

4.2.5. 2-(Bromomethyl-4-(tert-butyl)-6-(2-phenylpropan-2-yl)phenol (3a)

The compound **3a** was synthesized according to a literature procedure. [25] To 20 ml of glacial acetic acid were added 4-(tert-butyl)-2-(2-phenylpropan-2-yl)phenol (4.03 g, 15 mmol) and parafomaldehyde (0.50 g, 16.7 mmol). The mixture was stirred for about 1 h until parafomaldehyde was totally dissolved. 12 mL of HBr solution (33% in acetic acid) was added dropwise. After stirring for 1 h, the reaction mixture was cooled to -30 °C until a white precipitate formed. The solid product was collected on a frit, washed with cold petroleum ether, dried in air to give the product (4.97 g, 13.8 mmol. 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 7.48 (d, J = 2.4 Hz, 1H, Ar*H*), 7.36–7.33 (m, 4H, Ar*H*), 7.30–7.27 (m, 1H, Ar*H*), 7.24 (d, J = 2.4 Hz, 1H, Ar*H*), 4.54 (br s, 1H, O*H*), 4.47 (s, 2H, CH_2Br), 1.69 (s, 6H, C(CH_3)$_2$Ph), 1.35 (s, 9H, C(CH_3)$_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ 150.09, 147.91, 143.08, 135.32, 129.45, 127.36, 126.29, 126.10, 125.27, 124.28, 42.12, 34.49, 31.72, 30.53, 29.82 ppm.

4.2.6. 2-(Bromomethyl-4-(tert-buty l)-6-(1,1-diphenylethyl)phenol (3b)

To 20 ml of glacial acetic acid were added 4-(tert-butyl)-2-(1,1-diphenylethyl)phenol (4.96 g, 15 mmol) and parafomaldehyde (0.50 g, 16.7 mmol). The mixture was stirred for about 1 h until parafomaldehyde was totally dissolved. 12 mL of HBr solution (33% in acetic acid) was added dropwise. After stirring for about 2 h, a white precipitate formed. The solid product was collected on a frit, washed with cold petroleum ether, dried in air to give the product (6.06 g, 14.3 mmol. 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 7.34–7.22 (m, 11H, Ar*H*), 6.87 (m, 1H, Ar*H*), 4.71 (br s, 1H, O*H*), 4.53 (s, 2H, CH_2Br), 2.21 (s, 3H, C(CH_3)Ph$_2$), 1.17 (s, 9H, C(CH_3)$_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ 150.35, 146.17, 143.04, 134.80, 128.78, 128.31, 127.74, 127.06, 126.50, 125.41, 51.50, 34.33, 31.47, 30.86, 28.94 ppm.

4.2.7. 2-(Bromomethyl)-4-(tert-butyl)-6-(trityl)phenol (3c)

The compound **3c** was synthesized according to a literature procedure. [16] To 40 mL of HBr solution (33% in acetic acid) were added 4-(tert-butyl)-2-(trityl)phenol (5.89 g, 15 mmol) and parafomaldehyde (1.35 g, 45 mmol). The flask was warmed to 70 °C. The reaction was stopped after 1 h when the solution was completely saturated and a white precipitate had formed. The solid product was collected on a frit, washed with cold petroleum ether, dried in air to give the product (5.86 g, 12.1 mmol. 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 7.32–7.25 (m, 10H, Ar*H*), 7.19–7.17 (m, 6H, Ar*H*), 7.06 (d, J = 1.7 Hz, 1H, Ar*H*), 4.68 (br s, 1H, O*H*), 4.50 (s, 2H, CH_2Br), 1.14 (s, 9H, C(CH_3)$_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ 150.61, 144.10, 142.70, 133.16, 131.09, 129.12, 128.10, 127.04, 126.86, 125.51, 63.16, 34.39, 31.47, 30.75 ppm.

4.2.8. Ligand 4a

To a solution of 1 (0.71 g, 5 mmol) and TEA (1.39 ml, 10 mmol) in THF (20 ml), 3a (3.61 g, 10 mmol) in THF (20 ml) was added dropwise, and the reaction mixture was stirred at room temperature for 3 h. Precipitate was removed by filtration and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on a silica column eluting with dichloromethane first and then methanol to afford the ligand 4a as a white solid (2.97 g, 4.2 mmol. 85% yield). $[\alpha]_D^{20}$ = +86.5 (c=0.4 in EA). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 9.82 (br s, 2H, O*H*), 7.29 (s, 2H, Ar*H*), 7.18–7.16 (d, J = 7.5 Hz, 4H, Ar*H*), 7.11–7.08 (t, J = 7.3 Hz, 4H, Ar*H*), 7.02–6.98 (t, J = 7.0 Hz, 2H, Ar*H*), 6.78 (s, 2H, Ar*H*), 3.54 (s, 4H, CH_2Ar), 2.39–2.37 (m, 2H, NC*HCH*N), 1.77 (s, 6H, NCH_3), 1.71–1.67 (m, 12H, C(CH_3)$_2$Ph), 1.71–1.67 (m, 4H, CH_2CH_2CHN, masked by C(CH_3)$_2$Ph peaks), 1.31 (s, 18H, C(CH_3)$_3$), 1.04–0.94 (m, 4H, $CH_2CH_2CH_2CH_2$) ppm. ^{13}C NMR

(101 MHz, CDCl3, 298 K): δ 153.75, 151.24, 140.05, 135.11, 127.41, 126.16, 124.69, 124.03, 123.27, 121.55, 60.60, 58.16, 42.07, 34.81, 34.20, 31.85, 29.50, 29.30, 25.32, 23.36 ppm. FT-IR (KBr) 3517 w, 3083 w, 3056 w, 3021 w, 2960s, 2934s, 2863 m, 2800 w, 1936 w, 1864 w, 1739 w, 1602 m, 1843s, 1462s, 1444s, 1361 m, 1292 m, 1222s, 1147 m, 1030 m, 878 w, 821 w, 768 m, 698 s. HRMS: for $[M+H]^+$, calculated 703.5197, found 703.5191.

4.2.9. Ligand 4b

Ligand **4b** was synthesized following the same procedures as described above for the synthesis of **4a**, with compounds **1** and **3b** as starting materials. Product **4b** was obtained as a white solid (3.32 g, 4.0 mmol. 80% yield). $[\alpha]_D^{20} = +163.0$ (c=0.4 in EA). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 10.06 (br s, 2H, O*H*), 7.25–7.07 (m, 20H, Ar*H*), 6.78 (s, 2H, Ar*H*), 6.51 (s, 2H, Ar*H*), 3.67 (d, *J* = 13.3 Hz, 2H, CH_2Ar), 3.56 (d, *J* = 13.6 Hz, 2H, CH_2Ar), 2.51–2.49 (m, 2H, NC*HCH*N), 2.19 (s, 6H, NCH_3), 1.98 (s, 6H, C(CH_3)Ph_2), 1.85–1.70 (m, 4H, CH_2CH_2CHN), 1.09 (s, 18H, C(CH_3)$_3$), 1.14–1.03 (m, 4H, $CH_2CH_2CH_2CH_2$, masked by tBu peaks) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ 153.86, 149.23, 139.90, 134.51, 128.76, 128.57, 128.43, 128.30, 127.55, 127.30, 126.46, 125.46, 124.33, 121.54, 60.94, 57.98, 52.06, 35.50, 34.03, 31.61, 27.76, 25.46, 24.01 ppm. FT-IR (KBr) 3514 w, 3084 w, 3055 w, 3019 w, 2950s, 2904 m, 2860 m, 2801 w, 1947 w, 1880 w, 1805 w, 1599 w, 1481s, 1444s, 1363 m, 1294 m, 1260 w, 1216 m, 1125 w, 1074 w, 1027 m, 880 w, 759 m, 699 s, 643 w. HRMS: for $[M+H]^+$, calculated 827.5510, found 827.5509.

4.2.10. Ligand 4c

Ligand 4c was synthesized following the same procedures as described above for the synthesis of 4a, with compounds 1 and 3c as starting materials. Product 4c was obtained as a white solid (3.86 g, 4.1 mmol. 81% yield). $[\alpha]_D^{20} = +245.0$ (c=0.4 in EA). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 10.02 (br s, 2H, O*H*), 7.25–7.08 (m, 32H, Ar*H*), 6.77 (s, 2H, Ar*H*), 3.56 (d, *J* = 13.9 Hz, 2H, CH_2Ar), 3.49 (d, *J* = 13.6 Hz, 2H, CH_2Ar), 2.30–2.28 (m, 2H, NC*HCH*N), 1.85 (s, 6H, NCH_3), 1.55–1.43 (m, 4H, CH_2CH_2CHN), 1.15 (s, 18H, C(CH_3)$_3$), 0.93–0.84 (m, 4H, $CH_2CH_2CH_2CH_2$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ 153.98, 146.32, 139.99, 132.93, 131.27, 127.56, 126.95, 125.39, 124.79, 121.69, 63.49, 60.46, 58.64, 34.78, 34.20, 31.72, 25.79, 25.57 ppm. FT-IR (KBr) 3531 w, 2085 w, 3055 w, 3028 w, 2952s, 2859s, 2800 w, 1950 w, 1808 w, 1598 m, 1495s, 1480s, 1445s, 1362 m, 1293 m, 1261 m, 1206 m, 1187 w, 1034 m, 881 m, 745 s, 700 s, 659 w, 636 w. HRMS: for $[M+H]^+$, calculated 951.5823, found 951.5823.

4.3. Preparation of Cu(II) complexes

A solution of ligand (0.5 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (0.5 mmol) in 20 ml of ethanol was stired for 3 h. The solvent was evaporated under reduced pressure. The residue was purified on a silica gel column chromatography using hexane and ethyl acetate (2:3) as eluent to give the respective complex as a green solid.

4.3.1. Ligand 4a/$Cu(OAc)_2{\cdot}H_2O$ complex

FT-IR (KBr) 3605 w, 3084 w, 3054 w, 3020 w, 2950s, 2904 m, 2864 m, 1941 w, 1867 w, 1799 w, 1600 m, 1493 m, 1466s, 1449s, 1412 m, 1361 m, 1296s, 1233 m, 1219 m, 1153 m, 1100 m, 1030 w, 1012 w, 995 w, 875 m, 831 m, 772 m, 700 s, 605 m, 551 m. HRMS: for $[C_{48}H_{64}CuN_2O_2+H]^+$, calculated 764.4437, found 764.4424.

4.3.2. Ligand 4b/$Cu(OAc)_2{\cdot}H_2O$ complex

FT-IR (KBr) 3605 w, 3083 w, 3054 w, 3027 w, 2947s, 2903 m, 2863 m, 1945 w, 1879 w, 1805 w, 1599 m, 1492 m, 1470s, 1444s, 1413 m, 1361 m, 1299s, 1259 m, 1218 m, 1027 m, 876 m, 755 m, 700 s, 627 m, 607 w, 572 w. HRMS: for $[C_{58}H_{68}CuN_2O_2+H]^+$, calculated 888.4750, found 888.4753.

4.3.3. Ligand 4c/$Cu(OAc)_2{\cdot}H_2O$ complex

FT-IR (KBr) 3527 w, 3084 w, 3053 m, 3028 m, 2949s, 2903 m, 2862 m, 1947 w, 1894 w, 1809 w, 1599 m, 1492 m, 1447s, 1410 m, 1361 m, 1303 m, 1279 m, 1212 m, 1183 m, 1033 m, 1011 m, 875 m, 814 w, 753 m, 741 m, 702 s, 640 m, 608 m, 580 w. HRMS: for $[C_{68}H_{72}CuN_2O_2+Na]^+$, calculated 1034.4882, found 1034.4843.

4.4. General procedure for catalytic enantioselective Henry reaction

A chiral ligand (0.06 mmol, 12 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (10 mg, 0.05 mmol, 10 mol%) were added with THF (2 ml) to a test tube. A deep green solution was formed after stirring for 0.5 h at room temperature. The reaction mixture was stirred in an oil bath at a given temperature for 20 mins. A specified aldehyde (0.5 mmol), nitroalkane (5 mmol) and TEA (8 ul, 0.05 mmol, 10 mol%) were added, and the reaction mixture was stirred for a prescriptive time. The solvent was removed under reduced pressure and the resulting mixture was purified by column chromatography on a silica column with a hexane/EtOAc (v/v, 4/1) eluant to afford the desired nitroaldol product. Enatiomeric excesses were determined by chiral HPLC analysis using a Chiralcel OD-H or Chiralcel AD-H column.

4.4.1. (S)-2-nitro-1-phenylethanol (7a)

An enantiomeric excess of 94% ee was determined by HPLC on a Chiralcel OD-H column. 254 nm, hexane/IPA = 93/7, flow rate: 1 ml·min^{-1}, retention time: 21.63 min (minor), 24.16 min (major). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 7.41–7.35 (m, 5H), 5.47 (d, *J* = 9.5 Hz, 1H), 4.62 (dd, *J* = 13.4, 9.6 Hz, 1H), 4.52 (dd, *J* = 13.3, 2.9 Hz, 1H), 2.82 (d, *J* = 3.0 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ 138.20, 129.19, 129.15, 126.07, 81.35, 71.15 ppm.

4.4.2. (S)-2-nitro-1-o-tolylethanol (7b)

An enantiomeric excess of 91% ee was determined by HPLC on a Chiralcel OD-H column. 254 nm, hexane/IPA = 95/5, flow rate: 1 ml·min^{-1}, retention time: 22.29 min (minor), 31.77 min (major). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 7.52–7.50 (m, 1H), 7.29–7.23 (m, 2H), 7.20–7.17 (m, 1H), 5.67 (dd, *J* = 9.7, 2.5 Hz, 1H), 4.54 (dd, *J* = 13.4, 9.7 Hz, 1H), 4.43 (dd, *J* = 13.4, 2.6 Hz, 1H), 2.74 (br s, 1H), 2.38 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ 136.32, 134.59, 131.01, 128.86, 126.93, 125.75, 80.35, 68.09, 19.03 ppm.

4.4.3. (S)-2-nitro-1-m-tolylethanol (7c)

An enantiomeric excess of 88% ee was determined by HPLC on a Chiralcel OD-H column. 254 nm, hexane/IPA = 93/7, flow rate: 1 ml·min^{-1}, retention time: 18.59 min (minor), 21.13 min (major). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 7.31–7.27 (m, 1H), 7.22 (m, 1H), 7.20–7.17 (m, 2H), 5.43 (d, *J* = 9.5 Hz, 1H), 4.61 (dd, *J* = 13.3, 9.6 Hz, 1H), 4.50 (dd, *J* = 13.3, 2.9 Hz, 1H), 2.78 (br s, 1H), 2.37 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ 139.03, 138.17, 129.86, 129.07, 126.71, 123.11, 81.39, 71.19, 21.55 ppm.

4.4.4. (S)-2-nitro-1-p-tolylethanol (7d)

An enantiomeric excess of 92% ee was determined by HPLC on a Chiralcel OD-H column. 254 nm, hexane/IPA =95/5, flow rate: 1 ml·min^{-1}, retention time: 29.91 min (minor), 35.46 min (major). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 7.28 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 5.41 (d, *J* = 9.3 Hz, 1H), 4.59 (dd, *J* = 13.3, 9.6 Hz, 1H), 4.48 (dd, *J* = 13.3, 3.1 Hz, 1H), 2.78 (br s, 1H), 2.36 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ 139.05, 135.29, 129.81, 125.99, 81.37, 71.03, 21.29 ppm.

4.4.5. (S)-1-(2-methoxyphenyl)-2-nitroethanol (7e)

An enantiomeric excess of 90% ee was determined by HPLC on a Chiralcel OD-H column. 254 nm, hexane/IPA = 95/5, flow rate: 1 ml·min^{-1}, retention time: 22.84 min (minor), 25.86 min (major). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 7.44 (d, *J* = 7.5 Hz, 1H), 7.33

(t, J = 7.9 Hz, 1H), 7.02 (t, J = 7.5 Hz, 1H), 6.91 (d, J = 8.2 Hz, 1H), 5.64 (s, 1H), 4.65 (dd, J = 13.1, 3.2 Hz, 1H), 4.58 (dd, J = 13.0, 9.2 Hz, 1H), 3.89 (s, 3H), 3.12 (d, J = 6.1 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ156.15, 129.96, 127.37, 126.07, 121.33, 110.68, 79.99, 68.00, 55.55 ppm.

4.4.6. (S)-1-(3-methoxyphenyl)-2-nitroethanol (7f)

An enantiomeric excess of 95% ee was determined by HPLC on a Chiralcel OD-H column. 254 nm, hexane/IPA = 93/7, flow rate: 1 ml·min^{-1}, retention time: 34.90 min (minor), 50.67 min (major). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 7.34–7.30 (m, 1H), 6.97–6.96 (m, 2H), 6.91–6.88 (m, 1H), 5.44 (d, J = 9.4 Hz, 1H), 4.60 (dd, J = 13.4, 9.6 Hz, 1H), 4.51 (dd, J = 13.4, 3.0 Hz, 1H), 3.82 (s, 3H), 2.83 (br s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ 160.21, 139.82, 130.28, 118.18, 114.54, 111.60, 81.33, 71.05, 55.47 ppm.

4.4.7. (S)-1-(4-methoxyphenyl)-2-nitroethanol (7 g)

An enantiomeric excess of 91% ee was determined by HPLC on a Chiralcel OD-H column. 254 nm, hexane/IPA = 93/7, flow rate: 1 ml·min^{-1}, retention time: 29.68 min (minor), 37.60 min (major). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 7.33 (d, J = 8.5 Hz, 2H), 6.93 (d, J = 8.6 Hz, 2H), 5.42 (d, J = 9.2 Hz, 1H), 4.51 (dd, J = 13.2, 9.6 Hz, 1H), 4.48 (dd, J = 13.2, 3.0 Hz, 1H), 3.82 (s, 3H), 2.70 (br s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ 160.23, 130.30, 127.43, 114.57, 81.39, 70.83, 55.51 ppm.

4.4.8. (S)-1-(2-chlorophenyl)-2-nitroethanol (7 h)

An enantiomeric excess of 85% ee was determined by HPLC on a Chiralcel OD-H column. 254 nm, hexane/IPA = 89/1, flow rate: 0.9 ml·min^{-1}, retention time: 69.16 min (minor), 71.38 min (major). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 7.59 (dd, J = 7.6, 1.5 Hz, 1H), 7.32–7.19 (m, 3H), 5.77 (d, J = 9.5 Hz, 1H), 4.60 (dd, J = 13.6, 2.3 Hz, 1H), 4.38 (dd, J = 13.6, 9.6 Hz, 1H), 3.01 (br s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ 135.61, 131.60, 130.06, 129.83, 127.73, 127.63, 79.42, 67.95 ppm.

4.4.9. (S)-1-(4-chlorophenyl)-2-nitroethanol (7i)

An enantiomeric excess of 93% ee was determined by HPLC on a Chiralcel OD-H column. 254 nm, hexane/IPA = 95/5, flow rate: 1 ml·min^{-1}, retention time: 28.28 min (minor), 33.09 min (major). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 7.40–7.34 (m, 4H), 5.47–5.45 (m, 1H), 4.58 (dd, J = 13.5, 9.4 Hz, 1H), 4.49 (dd, J = 13.5, 2.9 Hz, 1H), 2.89–2.87 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ 136.63, 134.96, 129.35, 127.45, 81.09, 70.42 ppm.

4.4.10. (S)-1-(2-bromophenyl)-2-nitroethanol (7j)

An enantiomeric excess of 90% ee was determined by HPLC on a Chiralcel OD-H column. 254 nm, hexane/IPA = 79/1, flow rate: 0.8 ml·min^{-1}, retention time: 78.50 min (minor), 81.22 min (major). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 7.66 (d, J = 7.7 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H), 5.80 (d, J = 9.5 Hz, 1H), 4.69 (dd, J = 13.6, 1.2 Hz, 1H), 4.43 (dd, J = 13.6, 9.7 Hz, 1H), 3.09 (br s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ 137.17, 133.09, 130.37, 128.31, 127.91, 121.54, 79.46, 70.12 ppm.

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

An enantiomeric excess of 90% ee was determined by HPLC on a Chiralcel OD-H column. 254 nm, hexane/IPA = 93/7, flow rate: 1 ml·min^{-1}, retention time: 24.14 min (minor), 29.89 min (major). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 7.53 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 5.43 (dd, J = 9.6, 2.4 Hz, 1H), 4.57 (dd, J = 13.4, 9.3 Hz, 1H), 4.49 (dd, J = 13.5, 3.1 Hz, 1H), 2.96 (br s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ 137.16, 132.32, 127.75, 123.10, 81.03, 70.47 ppm.

4.4.12. (S)-2-nitro-1-(2-nitrophenyl)ethanol (7l)

An enantiomeric excess of 95% ee was determined by HPLC on a Chiralcel OD-H column. 254 nm, hexane/IPA = 95/5, flow rate: 1 ml·min^{-1}, retention time: 30.36 min (minor), 32.48 min (major). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 8.08 (d, J = 8.2 Hz, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.75 (t, J = 7.5 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 6.06 (d, J = 8.7 Hz, 1H), 4.87 (dd, J = 13.8, 1.6 Hz, 1H), 4.56 (dd, J = 13.8, 9.0 Hz, 1H), 3.20 (br s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ 147.26, 134.54, 134.13, 129.82, 128.82, 125.15, 80.18, 66.90 ppm.

4.4.13. (S)-2-nitro-1-(4-nitrophenyl)ethanol (7 m)

An enantiomeric excess of 90% ee was determined by HPLC on a Chiralcel OD-H column. 254 nm, hexane/IPA = 90/10, flow rate: 1 ml·min^{-1}, retention time: 24.18 min (minor), 29.04 min (major). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 8.26 (d, J = 8.7 Hz, 2H), 7.64 (d, J = 8.7 Hz, 2H), 5.62 (dd, J = 8.1, 4.1 Hz, 1H), 4.61 (dd, J = 12.5, 7.0 Hz, 1H), 4.57 (dd, J = 12.5, 2.8 Hz, 1H), 3.28 (br s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ 148.23, 145.11, 127.08, 124.31, 80.72, 70.09 ppm.

4.4.14. (S)-1-(naphthalen-1-yl)-2-nitroethanol (7n)

An enantiomeric excess of 90% ee was determined by HPLC a Chiralcel OD-H column. 254 nm, hexane/IPA = 90/10, flow rate: 1 ml·min^{-1}, retention time: 19.61 min (minor), 27.74 min (major). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 8.03 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 7.2 Hz, 1H), 7.61–7.49 (m, 3H), 6.25–6.23 (m, 1H), 4.68 (dd, J = 12.2, 2.5 Hz, 1H), 4.63 (dd, J = 12.2, 7.1 Hz, 1H), 2.99 (s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ 133.84, 133.67, 129.67, 129.51, 129.42, 127.19, 126.21, 125.62, 123.97, 121.95, 80.89, 68.43 ppm.

4.4.15. (S)-1-(naphthalen-2-yl)-2-nitroethanol (7o)

An enantiomeric excess of 88% ee was determined by HPLC on a Chiralcel OD-H column. 254 nm, hexane/IPA = 87/13, flow rate: 1 ml·min^{-1}, retention time: 32.18 min (minor), 49.12 min (major). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 7.81–7.79 (m, 4H), 7.48–7.36 (m, 3H), 5.57–5.52 (m, 1H), 4.65–4.60 (m, 1H), 4.54–4.48 (m, 1H), 2.93 (br s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ 135.55, 133.57, 133.34, 129.15, 128.20, 127.92, 126.85, 126.82, 125.46, 123.33, 81.32, 71.30 ppm.

4.4.16. (S)-1-cyclohexyl-2-nitro-ethanol (7p)

An enantiomeric excess of 94% ee was determined by HPLC on a Chiralcel AD-H column. 254 nm, hexane/IPA = 95/5, flow rate: 0.6 ml·min^{-1}, retention time: 32.46 min (minor), 34.87 min (major). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 4.49 (dd, J = 13.1, 2.9 Hz, 1H), 4.42 (dd, J = 13.1, 8.9 Hz, 1H), 2.40 (d, J = 5.0 Hz, 1H), 1.85–1.76 (m, 3H), 1.71–1.65 (m, 2H), 1.52–1.43 (m, 1H), 1.29–1.07 (m, 5H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ 79.45, 72.98, 41.58, 28.99, 28.12, 26.25, 26.05, 25.91 ppm.

4.4.17. (1S,2S)-2-Nitro-1-phenyl-propan-1-ol (8a)

The enantiomeric excess values (92% ee and 67% ee) were determined by HPLC on a Chiralcel AD-H column. 254 nm, hexane/IPA = 90/10, flow rate: 1 ml·min^{-1}, retention time: 8.89 min (*anti,* major), 9.96 min (*anti,* minor), 11.60 min (*syn,* major), 12.67 min (*syn,* minor). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 7.41–7.36 (m, 5H), 5.41 (t, J = 3.4 Hz, 0.4H, *anti*), 5.04 (dd, J = 9.2, 3.8 Hz, 0.6H, *syn*), 4.81–4.74 (m, 0.6H, *syn*), 4.73–4.67 (m, 0.4H, *anti*), 2.63 (s, 0.4H, *anti*), 2.49 (s, 0.6H, *syn*), 1.51 (d, J = 6.8 Hz, 1.2H, *anti*), 1.33 (d, J = 6.8 Hz, 1.8H, *syn*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ 138.40, 129.38, 129.17, 128.90, 128.69, 127.05, 126.08, 88.53, 87.55, 76.43, 74.01, 16.63, 12.23 ppm.

4.4.18. (1S,2S)-2-Nitro-1-p-tolyl-propan-1-ol (8d)

The enantiomeric excess values (95% ee and 73% ee) were determined by HPLC on a Chiralcel AD-H column. 254 nm, hexane/IPA = 95/5, flow rate: 0.6 ml·min^{-1}, retention time: 29.78 min (*anti,* major), 33.89 min (*anti,* minor), 46.35 min (*syn,* major), 54.77 min (*syn,* minor). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 7.27–7.25 (m, 2H), 7.22–7.18 (m, 2H), 5.34 (s, 0.39H, *anti*), 4.99 (dd, J = 9.1, 2.9 Hz, 0.61H, *syn*), 4.79–4.72 (m, 0.61H, *syn*), 4.71–4.65 (m, 0.39H, *anti*), 2.60 (s, 0.39H, *anti*), 2.45 (s, 0.61H, *syn*), 2.36 (s, 1.83H, *syn*), 2.35 (s, 1.17H, *anti*), 1.51 (d, J = 6.8 Hz, 1.17H, *anti*), 1.31 (d, J = 6.8 Hz, 1.83H, *anti*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ139.27, 138.50, 135.59, 135.46, 129.80, 129.53, 126.94, 126.00, 88.57, 87.64, 76.27, 74.04, 21.31, 21.26, 16.60, 12.39 ppm.

4.4.19. (1S,2S)-1-(4-Methoxy-phenyl)-2-nitro-propan-1-ol (8 g)

The enantiomeric excess values (95% ee and 60% ee) were determined by HPLC on a Chiralcel AD-H column. 254 nm, hexane/IPA = 90/10, flow rate: 0.6 ml·min^{-1}, retention time: 26.34 min (*anti,* major), 29.40 min (*anti,* minor), 36.61 min (*syn,* major), 41.50 min (*syn,* minor). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 7.29 (d, J = 8.6 Hz, 2H), 6.93–6.90 (m, 2H), 5.31 (t, J = 3.2 Hz, 0.33H, *anti*), 4.99 (dd, J = 9.1, 2.8 Hz, 0.67H, *syn*), 4.78–4.71 (m, 0.67H, *syn*), 4.70–4.64 (m, 0.33H, *anti*), 3.82 (s, 2.01H, *syn*), 3.81 (s, 0.99H, *anti*), 2.57 (s, 0.33H, *anti*), 2.42 (s, 0.67H, *syn*), 1.53 (d, J = 6.8 Hz, 0.99H, *anti*), 1.31 (d, J = 6.8 Hz, 2.01H, *syn*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ 160.33, 159.85, 130.62, 130.50, 128.30, 127.39, 114.53, 114.27, 88.64, 87.71, 76.06, 73.91, 55.48, 55.45, 16.63, 12.63 ppm.

4.4.20. (1S,2S)-1-(4-Chloro-phenyl)-2-nitro-propan-1-ol (8i)

The enantiomeric excess values (96% ee and 80% ee) were determined by HPLC on a Chiralcel AD-H column. 254 nm, hexane/IPA = 94/6, flow rate: 1 ml·min^{-1}, retention time: 12.99 min (*anti,* major), 14.38 min (*anti,* minor), 18.71 min (*syn,* minor), 20.71 min (*syn,* major). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 7.40–7.31 (m, 4H), 5.39 (s, 0.31H, *anti*), 5.03 (d, J = 8.9 Hz, 0.69H, *syn*), 4.76–4.69 (m, 0.69H, *syn*), 4.68–4.63 (m, 0.31H, *anti*), 2.73 (s, 0.31H, *anti*), 2.60 (s, 0.69H, *syn*), 1.49 (d, J = 6.8 Hz, 0.93H, *anti*), 1.33 (d, J = 6.9 Hz, 2.07H, *syn*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ 136.98, 136.85, 135.16, 134.46, 129.32, 129.05, 128.39, 127.48, 88.28, 87.31, 75.61, 73.33, 16.47, 12.14 ppm.

4.4.21. (1S,2S)-1-Naphthalen-1-yl-2-nitro-propan-1-ol (8n)

The enantiomeric excess values (94% ee and 44% ee) were determined by HPLC on a Chiralcel AD-H column. 254 nm, hexane/IPA = 94/6, flow rate: 1 ml·min^{-1}, retention time: 12.81 min (*anti,* major), 16.63 min (*anti,* minor), 23.31 min (*syn,* major), 27.42 min (*syn,* minor). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 8.30 (d, J = 8.4 Hz, 1H), 7.93–7.88 (m, 2H), 7.62–7.49 (m, 4H), 6.31 (s, 0.08H, *anti*), 5.82 (dd, J = 9.1, 3.4 Hz, 0.92H, *syn*), 5.18–5.11 (m, 0.92H, *syn*), 4.96–4.91 (m, 0.08H, *anti*), 2.64 (s, 1H), 1.45 (d, J = 6.8 Hz, 0.24H, *anti*), 1.28 (d, J = 6.9 Hz, 2.76H, *syn*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): (*syn*) δ 134.13, 134.08, 130.92, 129.91, 129.29, 126.96, 126.24, 125.77, 125.48, 123.32, 88.60, 73.84, 16.95 ppm.

4.4.22. (1S,2S)-1-Naphthalen-2-yl-2-nitro-propan-1-ol (8o)

The enantiomeric excess values (96% ee and 77% ee) were determined by HPLC on a Chiralcel AD-H column. 254 nm, hexane/IPA = 90/10, flow rate: 0.6 ml·min^{-1}, retention time: 25.73 min (*anti,* major), 29.21 min (*anti,* minor), 39.37 min (*syn,* major), 44.91 min (*syn,* minor). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 7.91–7.85 (m, 4H), 7.55–7.44 (m, 3H), 5.59 (s, 0.33H, *anti*), 5.21 (dd, J = 9.0, 3.2 Hz, 0.67H, *syn*), 4.93–4.85 (m, 0.67H, *syn*), 4.84–4.78 (m, 0.33H, *anti*), 2.87 (s, 0.33H, *anti*), 2.63 (s, 0.67H, *syn*), 1.53 (d, J = 6.8 Hz, 0.99H, *anti*), 1.35 (d, J = 6.9 Hz, 2.01H, *syn*) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 298 K): δ 135.72, 133.68, 133.31, 133.20, 129.18, 128.74, 128.19, 127.91, 127.85, 126.87, 126.83, 126.79, 126.68, 126.59, 125.41, 123.95, 123.44, 88.47, 87.43, 76.56, 74.10, 16.65, 12.15 ppm.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2020.121546.

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