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Asymmetric Henry reactions catalyzed by metal complexes of chiral oxazoline based ligands

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We dedicate this paper to the memory of Professor Dr. Ayhan S. DEMIR who died on 24 June 2012

ABSTRACT

Chiral oxazolines have been synthesized from norephedrine and pyrrole nitrile or benzoyl chloride and applied to the catalytic asymmetric Henry reactions of *p*-nitro aldehydes with nitromethane to provide β-hydroxy nitroalkanols in high conversion (up to 92%). The reaction was then optimized in terms of the metal, solvent, temperature, and amount of chiral ligand. The corresponding catalyst with $Cu(OTf)_2$ and isopropanol as the solvent gave the best enantioselectivities (up to 84% ee) of the corresponding β-nitroalkanol for *p*-nitrobenzaldehyde.

1. Introduction

The Henry reaction is an important organic reaction involving the formation of a C–C bond.[1] The resulting product of this reaction is a β-nitro alcohol, which can be converted into the essential building blocks of natural products or pharmaceuticals such as β-amino alcohols, aziridines, α-hydroxy carboxylic acids, α-hydroxy ketones, α-nitro ketones, aldehydes, and sulfides.[2] Shibasaki reported the first asymmetric version of the Henry reaction in 1992.[3] Since then, a very large number of chiral catalysts containing chiral ligands with metal atoms and also organocatalyst have been synthesized and applied to the asymmetric Henry reaction.[4]

Oxazolines are an important class of heterocyclic compounds and are versatile intermediates in synthetic organic chemistry.[5] These compounds are used as protecting groups for carboxylic acids[6] and hydroxylamines. Chiral oxazolines have also been extensively used in asymmetric syntheses as both auxiliaries and ligands.[7]

A very large number of chiral ligands containing one or more oxazoline rings have been synthesized and employed to prepare enantiomerically pure compounds using chiral ligands in many metal-catalyzed asymmetric reactions. Examples of widely used ligands of this type are pyridinooxazoline,[8] bisoxazoline,[9] bisoxazolinopyridine,[10] BINOL-oxazoline,[11] and phosphine-oxazoline[12] derivatives. These chiral ligands have been applied to a wide range of catalytic reactions including hydrosilylations[13] Diels Alders reactions,[14] cyclopropanations,[10a,15] allylic alkylation,[16] enantioselective diethylzinc additions to aldehydes,[17] and the asymmetric Henry reactions.[18] Du et al.[19] reported the synthesis of chiral aminophenyloxazoline and oxazoline-Schiff base and their applications in enantioselective Henry reactions. When aminophenyl oxazoline ligands were used as a ligand with $Cu(OAc)_2$ in the Henry reaction of *p*-nitrobenzaldehyde, the corresponding products were obtained in moderate chemical yields (67–72%) but with low enantioselectivities (21–46% ee).

In contrast to the large number of chiral pyridyl oxazolines and bisoxazolines used as ligands for metal catalyzed asymmetric reactions, only a few examples of chiral pyrrole oxazoline ligands have been reported so far. The first chiral pyrrole oxazoline ligands that used free pyrrole nitrogen were synthesized and applied to copper-catalyzed asymmetric cyclopropanations by Brunner in 1998. However, the corresponding product was obtained with low enantiomeric excess (3–14% ee).[20]

To the best of our knowledge, chiral oxazolines containing a pyrrole ring have not been used before as ligands in Henry reactions. Herein we report their first application in this reaction. We synthesized chiral oxazoline-based ligands from pyrrole-2-carbonitrile and 2-hydroxy benzoyl chloride. The chiral ligands synthesized were applied as catalysts in Cu-catalyzed asymmetric Henry reactions. Under the optimized conditions, aromatic and aliphatic aldehydes gave the corresponding products in moderate to good yields and with high enantioselectivities. Moreover, when nitroethane was used instead of nitromethane in the asymmetric Henry reaction, products with two stereogenic centers were obtained successfully.

2. Result and discussion

2.1. Preparation of chiral 2-oxazoline ligand

A number of methods have been developed for the preparation of 2-oxazolines from carboxylic acid,[21] esters,[22] nitriles,[23]

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aldehydes,[24] amino alcohols,[25] and hydroxyamides.[26] Herein chiral 2-oxazolines **3a**,**b** and **4a**,**b** were synthesized from both enantiomers of norephedrine with pyrrole-2-carbonitrile or an acyl chloride by the two methods shown in Schemes 1 and 2, respectively. In the retrosynthetic plan in Scheme 1, pyrrole was formylated by the Vilsmeier Haack method[27] and the formylated pyrrole (75% yield) was treated with NMP, $NH_2OH{\cdot}HCl$ to form pyrrole-2-carbonitrile **1**[28] (70% yield). In the first method used for the chiral oxazoline ligands, pyrrole-2-carbonitrile was treated with both enantiomers of norephedrine **2** to give ligand **3** as shown in Scheme 1.[29] The stereochemistry of the starting material was maintained throughout the course of the reaction; thus, (1*R*,2*S*)-norephedrine gave (4*S*,5*R*)-**3a**, while (1*S*,2*R*)-norephedrine gave (4*R*,5*S*)-**3b** (Cl, C2 in the starting material corresponds to C5, C4 in the product). Ligands (4*S*,5*R*)-**3a** and (4*R*,5*S*)-**3b** were obtained by using (1*R*,2*S*)- and (1*S*,2*R*)-norephedrine **2a**,**b** in 68% and 63% yields, respectively. The synthesis of pyrrole oxazoline (4*S*,5*R*)-**3a** was performed from the corresponding starting materials using activated $ZnCl_2$ in chlorobenzene at 80 °C with 29% yield using the method reported by Brunner et al.[20a]

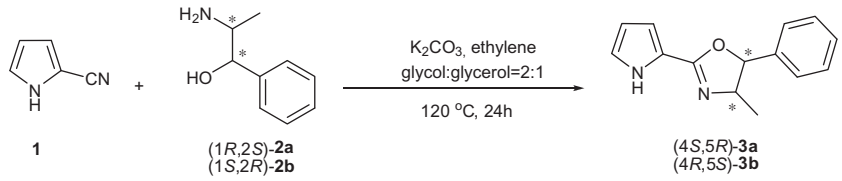
In the second method used for chiral ligands (Scheme 2), salicylic acid was reacted with thionyl chloride to give 2-hydroxybenzoyl chloride. Without further purification, the acid chloride was treated with both enantiomers of norephedrine **2a** and **2b** and Et_3N in CH_2Cl_2 and then refluxed under basic conditions to yield oxazolines (4*S*,5*R*)-**4a** and (4*R*,5*S*)-**4b**.

2.2. Enantioselective Henry reactions

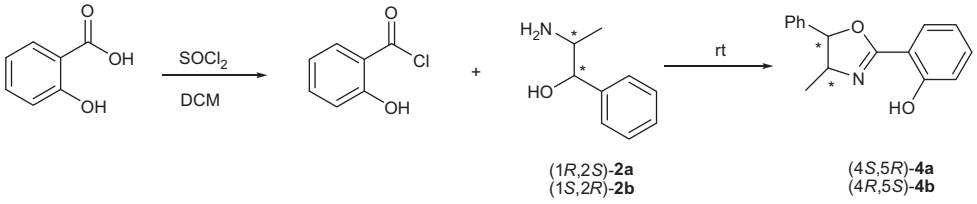
We examined the catalytic performance of these chiral oxazoline based ligands in the enantioselective Henry reaction. For this purpose, *p*-nitrobenzaldehyde and nitromethane were selected as the model substrate and nitroalkane (Scheme 3). The reaction was performed in THF in the presence of 10 mol % chiral ligand at room temperature. As can be seen from Table 1, the addition of CH_3NO_2 to *p*-nitrobenzaldehyde led to the corresponding product in 57–75% yield with 2-46% ee. In the presence of only a chiral ligand, the observed enantioselectivities were very low. Compound (4*S*,5*R*)-**3a**, which has an (*R*)-configuration at the oxygen bearing stereogenic center gave the (*S*)-product, whereas (4*R*,5*S*)-**3b** with an (*S*)-configuration at the same stereogenic center, gave the (*R*)-product. Thus, ligands (4*S*,5*R*)-**3a** and (4*S*,5*R*)-**4a** induced enantiomeric excess in the (*S*)-configured product, while (4*R*,5**S**)-**3b** and (4*R*,5*S*)-**4b** led to enantiomeric excess in the (*R*)-configured product. These results indicate that the configuration of the chiral β-nitroalkanol depends on the configuration of the oxygen bearing stereogenic center. The enantiomeric oxazoline ligand pairs induced an opposite enantioselectivity in the Henry reaction (Table 1, entries 1–2, 3–4).

With the aim of improving the enantioselectivity different procedures were tested and the results are summarized in Table 1. We next attempted to improve further the enantioselectivity using Et_2Zn. Trost reported the first dinuclear zinc-amino alcohol catalyzed asymmetric Henry reaction and the corresponding products were obtained with high enantiomeric excess and yields (up to 93% ee and 90% yield).[30] Since then, several zinc catalytic systems such as *N*-methylephedrine-Zn,[31] bicyclo[3.3.0]octane based β-amino alcohol-Zn,[32] ferrocenyl-substituted aziridinylmethanol-Zn,[33] and brucine-derived amino alcohol-Zn[34] have been prepared for asymmetric Henry reactions and afforded poor to good enantioselectivities but with moderate chemical yields.

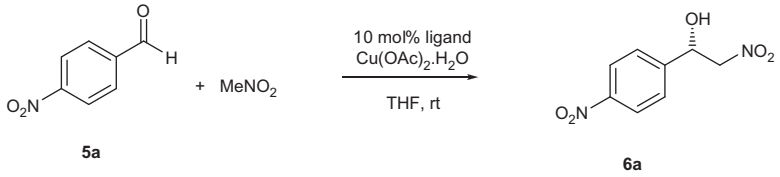
A solution of Et_2Zn was added to a solution of the chiral 2-oxazoline ligands **3a**,**b** and **4a**,**b** in dry toluene at 0 °C under an atmosphere of nitrogen and then stirred for 30 min to form chiral zinc-catalyst at 0 °C. Next, CH_3NO_2 and *p*-nitrobenzaldehyde were added into the mixture. The reaction mixture was stirred at room temperature for 48 h to give 2-nitro-1-(4-nitrophenyl)ethanol in moderate yield and with low ee in the presence of (4*S*,5*R*)-**3a** or



Scheme 1. Synthesis of chiral oxazoline ligands (4*S*,5*R*)-**3a** and (4*R*,5*S*)-**3b**.

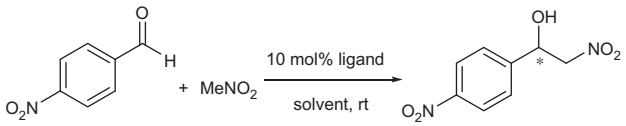


Scheme 2. Synthesis of chiral oxazoline ligands (4*S*,5*R*)-**4a** and (4*R*,5*S*)-**4b**.



Scheme 3. Henry reaction of nitromethane with *p*-nitrobenzaldehyde.

Table 1
Enantioselective Henry reaction of nitromethane with *p*-nitrobenzaldehyde under different reaction conditions[a]



5a **6a**

Entry	Ligand	Method	Yield[e] (%)	ee (%)	Conf[f]
1	(4*S*,5*R*)-**3a**	Ligand[b]	57	30	(*S*)
2	(4*R*,5*S*)-**3b**	Ligand[b]	59	25	(*R*)
3	(4*S*,5*R*)-**4a**	Ligand[b]	72	43	(*S*)
4	(4*R*,5*S*)-**4b**	Ligand[c]	75	46	(*R*)
5	(4*S*,5*R*)-**3a**	Et_2Zn–ligand[c]	66	8	(*S*)
6	(4*R*,5*S*)-**3b**	Et_2Zn–ligand[c]	64	4	(*R*)
7	(4*S*,5*R*)-**4a**	Et_2Zn–ligand[c]	65	51	(*S*)
8	(4*R*,5*S*)-**4b**	Et_2Zn–ligand[c]	63	47	(*R*)
9	(4*S*,5*R*)-**3a**	$Cu(OAc)_2{\cdot}H_2O$–Ligand[d]	53	51	(*S*)
10	(4*R*,5*S*)-**3b**	$Cu(OAc)_2{\cdot}H_2O$–Ligand[d]	66	53	(*R*)
11	(4*S*,5*R*)-**4a**	$Cu(OAc)_2{\cdot}H_2O$–Ligand[d]	58	75	(*S*)
12	(4*R*,5*S*)-**4b**	$Cu(OAc)_2{\cdot}H_2O$–Ligand[d]	61	69	(*R*)

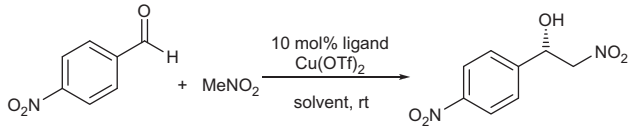
[a] The reactions were carried out with 1 mmol of *p*-nitro benzaldehyde and 10 mmol nitromethane in 2 mL of THF in the presence of 10 mol % ligand at room temperature for 48 h.
[b] With 10 mol % ligand, entries 1–4.
[c] With 10 mol % ligand and 3 mmol Et_2Zn, entries 5–8.
[d] With 10 mol % ligand, and $Cu(OAc)_2$ entries 9–12.
[e] Values are isolated yields after chromatographic purification.
[f] Enantiomeric excesses were determined by HPLC using a Chiralcel OD-H column. The absolute configuration was determined by comparison of the retention time (chiral HPLC) with the literature values.[10e,4k,l]

(4*R*,5*S*)-**3b** (Table 1, entry 5, 6). As shown in Table 1, the best results were obtained using (4*S*,5*R*)-**4a** (65% yield, 51% ee) and (4*R*,5*S*)-**4b** (63% yield, 47% ee).

To increase the yield and enantioselectivity of the chiral 2-nitro-1-(4-nitrophenyl) ethanol **6a**, $Cu(OAc)_2{\cdot}H_2O$ was used as the metal source. The combination of ligand (4*S*,5*R*)-**3a** with $Cu(OAc)_2{\cdot}H_2O$ gave the product in 53% yield with 51% ee for the major (*S*)-enantiomer (Table 1, entry 9). In the presence of (4*R*,5*S*)-**3b**, the corresponding product was obtained in 66% yield with 53% ee for the major (*R*)-enantiomer (entry 10). Ligands (4*S*,5*R*)-**4a** and (4*R*,5*S*)-**4b** gave nitroalkanols **6a** with a higher enantimeric excess (75% and 69%, respectively) (entries 11, 12). In order to determine the optimum reaction conditions, the effect of different reaction parameters, such as the metal source, solvent, catalyst loading, and reaction temperature, were investigated by using chiral ligands (4*S*,5*R*)-**3a,** (4*R*,5*S*)-**3b** and (4*S*,5*R*)-**4a**.

The effects of various metal sources were examined using ligands (4*S*,5*R*)-**3a**, (4*R*,5*S*)-**3b** and (4*S*,5*R*)-**4a**. The results are summarized in Table 2. When the reaction was performed with $Ni(OAc)_2{\cdot}H_2O$, $Zn(OAc)_2{\cdot}H_2O$, $Zn(OTf)_2$, $CoCl_2{\cdot}2H_2O$, and $NiCl_2{\cdot}6H_2O$, the product was obtained in moderate to good yield, but with low ee values (Table 2, entries 2–6). In the presence of 10 mol % $Cu(OTf)_2$ and ligands (4*S*,5*R*)-**4a**, (4*S*,5*R*)-**3a**, and (4*R*,5*S*)-**3b**, the corresponding products were obtained in 79%, 80%, and 78% yield with 70%, 58%, and 59% ee, respectively (entries 7–9). By keeping the ligand (4*S*,5*R*)-**4a** ratio at 10 mol % and reducing the $Cu(OTf)_2$ ratio from 10 to 5 mol %, the enantioselectivity increased to 75% ee, without any changes in the yield (entries 7, 10). When ligands (4*S*,5*R*)-**3a** and (4*R*,5*S*)-**3b** were used as catalysts, the nitroalkanols were obtained in 81% and 78% yields with 65% and 63% ee, respectively (entries 11, 12). As shown in Table 2, the most suitable ratio of metal to ligand proved to be 1:2 (entries 7, 10).

Table 2
Screening metal salts in the asymmetric Henry reaction[a]



5a **6a**

Entry	Metal salt	Ligand	Metal salt: ligand	Yield[b] (%)	ee[c] (%)
1	$Cu(OAc)_2{\cdot}H_2O$	(4*S*,5*R*)-**4a**	1:1	58	75
2	$Ni(OAc)_2{\cdot}H_2O$	(4*S*,5*R*)-**4a**	1:1	70	12
3	$Zn(OAc)_2{\cdot}H_2O$	(4*S*,5*R*)-**4a**	1:1	75	15
4	$Zn(OTf)_2$	(4*S*,5*R*)-**4a**	1:1	75	27
5	$CoCl_2{\cdot}2H_2O$	(4*S*,5*R*)-**4a**	1:1	69	42
6	$NiCl_2{\cdot}6H_2O$	(4*S*,5*R*)-**4a**	1:1	59	29
7	$Cu(OTf)_2$	(4*S*,5*R*)-**4a**	1:1	79	70
8[d]	$Cu(OTf)_2$	(4*S*,5*R*)-**3a**	1:1	80	58
9	$Cu(OTf)_2$	(4*R*,5*S*)-**3b**	1:1	78	59
10[d]	$Cu(OTf)_2$	(4*S*,5*R*)-**4a**	1:2	80	75
11[d]	$Cu(OTf)_2$	(4*S*,5*R*)-**3a**	1:2	81	65
12[d]	$Cu(OTf)_2$	(4*R*,5*S*)-**3b**	1:2	78	63

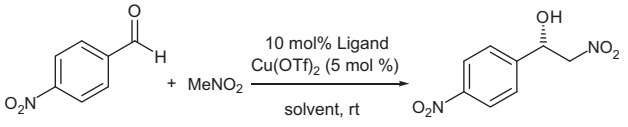
[a] The reactions were carried out with 1 mmol of *p*-nitrobenzaldehyde and 10 mmol of nitromethane in 2 mL of THF in the presence of 10 mol % ligand and 10 mol % metal salt at room temperature.
[b] Values are isolated yields after chromatographic purification.
[c] Enantiomeric excesses were determined by HPLC using a Chiralcel OD-H column.
[d] With 10 mol % ligand and 5 mol % $Cu(OTf)_2$, entries 9 and 13.

Solvents always play an important role with regard to the enantioselectivity. The influence of different solvents, such as EtOH, MeOH, THF, ^{i}PrOH, DCM, and toluene were tested in the enantioselective Henry reaction between *p*-nitrobenzaldehyde and nitromethane in combination with $Cu(OAc)_2.H_2O$ and ligand (4*S*,5*R*)-**4a**. As can be seen in Table 3, protic solvents (MeOH, EtOH, and ^{i}PrOH) proved to be better than aprotic solvents (THF and DCM), giving higher enantiomeric excesses (entries 1, 2, 4 and 3, 5). The highest enantiomeric excess (82%) was observed in ^{i}PrOH. The use of the aprotic solvent DCM gave 39% enantiomeric excess. The lowest enantiomeric excess (25%) was observed when toluene was used as the solvent. It was found that the enantioselectivity increased in the order MeOH < EtOH < ^{i}PrOH (Table 3). It is possible that these alcoholic solvents might coordinate with the copper metal, and this process could increase the enantioselectivity. The low chemical yields and enantioselectivities could be explained using non-coordinating solvents such as DCM, and toluene. In the presence of (4*S*,5*R*)-**3a**, the nitroalkanol **6a** was obtained in 84% yield with 65% ee (Table 3, entry 8).

Since the reaction temperature has a significant effect on the chemical yield and ee values of the nitroaldol product,[35] the optimization of temperature was carried out. Decreasing the temperature of the reaction from room temperature to 0 °C, caused the ee value to increase considerably (Table 3, entries 9, 10). The asymmetric Henry reaction was performed using (4*S*,5*R*)-**4a** at 0 °C and the highest enantioselectivity was obtained with an (*S*)-configuration in 84% ee (entry 9). However, at −20 °C, the selectivity was decreased (Table 3, entries 10, 12).

It has been reported that a chiral catalyst in the presence of base has an enhancement effect on the enantioselectivity.[4e,k,8a,10d,36] Therefore, a series of experiments were performed by using a base, such as K_2CO_3, DBU, Et_3N, DMAP, DBU, Na_2CO_3, and DABCO. These bases were tested in the reaction between *p*-nitrobenzaldehyde and nitromethane in the presence of 10 mol % ligand, 5 mol % $Cu(OTf)_2$, and 50 mol % base. As can be seen in Table 4, when

Table 3
Effects of the solvents and reaction temperature on the asymmetric Henry reaction[a]



5a 6a

Entry	Ligand	Solvent	Temp. (°C)	Yield[b] (%)	ee[c] (%)
1	(4*S*,5*R*)-**4a**	EtOH	rt	75	80
2	(4*S*,5*R*)-**4a**	MeOH	rt	75	78
3	(4*S*,5*R*) **4a**	THF	rt	80	75
4	(4*S*,5*R*)-**4a**	^{i}PrOH	rt	92	82
5	(4*S*,5*R*)-**4a**	DCM	rt	75	39
6	(4*S*,5*R*)-**4a**	Toluene	rt	51	25
7	(4*S*,5*R*)-**4a**	MeCN	rt	68	56
8	(4*S*,5*R*)-**3a**	^{i}PrOH	rt	81	65
9	(4*S*,5*R*)-**4a**	^{i}PrOH	0	80	84
10	(4*S*,5*R*)-**4a**	^{i}PrOH	−20	83	68
11	(4*S*,5*R*)-**3a**	^{i}PrOH	0	84	76
12	(4*S*,5*R*)-**3a**	^{i}PrOH	−20	78	52

[a] The reactions were carried out with 1 mmol of *p*-nitro benzaldehyde and 10 mmol of nitromethane in 2 mL of solvent in the presence of 10 mol % ligand and 5 mol % metal salt.
[b] Values are isolated yields after chromatographic purification.
[c] Enantiomeric excesses were determined by HPLC using a Chiralcel OD-H column.

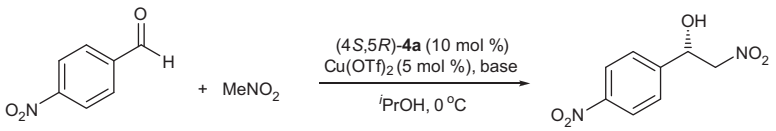
K_2CO_3, DBU, or Et_3N were used as the base, the yield of the asymmetric Henry reaction increased while the ee value decreased (entries 2, 3, and 4). Bases such as DIPEA and DMAP gave the product in low yields but with moderate enantiomeric excess (entries 5, 6). Bases such as Na_2CO_3 and DABCO gave the highest yield although the ee values are moderate (Table 4, entries 7, 8).

The asymmetric Henry reaction was performed with different aromatic aldehydes with electron-withdrawing and electron-donating substituents under the optimized conditions: 10 and, 5 mol % $Cu(OTf)_2$ in ^{i}PrOH for ligands (4*S*,5*R*)-**3a** (4*R*,5*S*)-**3b**, and (4*S*,5*R*)-**4a**. The results are summarized in Table 5. Both chiral ligands (4*S*,5*R*)-**3a** and (4*R*,5*S*)-**3b** afforded the opposite enantiomers with all of the aldehydes tested, that is while ligand (4*S*,5*R*)-**3a** afforded the (*S*)-enantiomer, the opposite (*R*)-enantiomer of the corresponding products was obtained with ligand (4*R*,5*S*)-**3b**. Electron-withdrawing substitutents gave higher enantioselectivities when compared to electron-donating substituents (Table 5). It is known that the presence of electron-withdrawing groups leads to an increase in the electrophilicity of carbonyl carbon atom in aryl aldehydes, while the presence of electron-donating groups decreases it. We expected that the substrates with an electron-with drawing substituent afforded a faster reaction leading to higher enantioselectivity. With both ligands, high enantiomeric excesses were observed for aromatic aldehydes bearing substituents at the *ortho* position. The reason for this appears to be more due to steric hindrance. In the presence of ligands (4*S*,5*R*)-**3a,** (4*R*,5*S*)-**3b**, and (4*S*,5*R*)-**4a**, the hetereoaromatic aldehyde furan-2-carbaldehyde also gave the nitroaldol product with 67%, 65%, and 85% ee, respectively (Table 5, entry 14). Next, the scope of the asymmetric Henry reaction was studied with aliphatic aldehydes using (4*S*,5*R*)-**3a** and (4*R*,5*S*)-**3b** and ligand (4*S*,5*R*)-**4a**. The aliphatic aldehydes provided the corresponding adduct with higher enantioselectivity than the aromatic aldehydes. For aliphatic aldehydes, the enantioselectivity increased with an increase in the chain length of the aldehydes. The branched aliphatic aldehydes afforded optically Henry adducts in moderate yield and with good enantiomeric excess.

The optimized catalyst was also applied to the diastereoselective Henry reaction with nitroethane used as the nucleophile.[38] As shown in Table 6, aliphatic aldehydes showed lower selectivity than aromatic aldehydes, under the optimized reaction conditions, all aldehydes (both aromatic and aliphatic) afforded the corresponding products in moderate to good diastereoselectivity. High enantioselectivities were obtained for the *syn*-products (up to 78%). *p*-Nitrobenzaldehyde led to the corresponding product in 72% yield with 65:35 *syn*:*anti* diastereoselectivity. Aldehydes with an electron-withdrawing subtitutent such as NO_2 showed lower diastereoselectivity than 2-methoxybenzaldehyde (Table 6, entries 1, 2). Isobutyraldehyde gave the corresponding product in 75% yield with 64:36 *syn*:*anti* selectivity, with 63% enantiomeric excess of the *syn*-product (Table 6, entry 3).

We propose a mechanism in which the aldehyde coordinates to the copper, followed by nucleophilic attack of CH_3NO_2 onto the less sterically hindered face of the carbonyl group, affording products with high enantioselectivity. We were unable to obtain crystals of the copper complexes with these ligands suitable for X-ray

Table 4
Effects of organic base on the asymmetric Henry reaction[a]

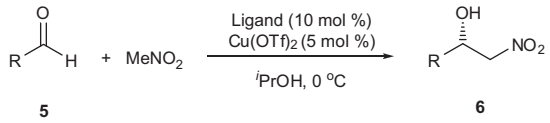


5a 6a

Entry	Base additive	Loading of base (mol %)	Yield[b] (%)	ee[c] (%)
1		—	80	92
2	K_2CO_3,	50	85	55
3	DBU	50	87	17
4	Et_3N	50	90	65
5	DIPEA	50	47	69
6	DMAP	50	53	62
7	Na_2CO_3	50	92	65
8	DABCO	50	95	62

[a] The reactions were carried out with 1 mmol of *p*-nitro benzaldehyde and 10 mmol of nitromethane in 2 mL of ^{i}PrOH in the presence of 10 mol % ligand, 5 mol % $Cu(OTf)_2$, and 50 mol % base at 0 °C.
[b] Values are isolated yields after chromatographic purification.
[c] Enantiomeric excesses were determined by HPLC using a Chiralcel OD-H column.

Table 5
Enantioselective Henry reaction of various aldehydes with nitromethane under optimal conditions[a]

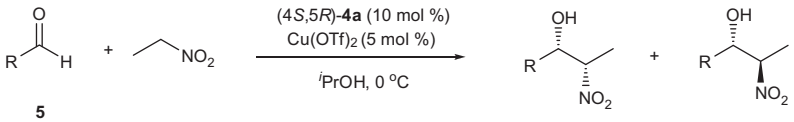


5 6

Entry	Aldehyde	Product **9**	(4*S*,5*R*)-**3a**		(4*R*,5*S*)-**3b**		(4*S*,5*R*)-**4a**	
			Yield[b] (%)	ee[c,d] (%)	Yield[b] (%)	ee[c,e] (%)	Yield[b] (%)	ee[c,d] (%)
1	4-$NO_2C_6H_4$	**6a**	80	76	84	74	80	84
2	2-$NO_2C_6H_4$	**6b**	75	78	83	76	83	86
3	PhCHO	**6d**	78	75	78	73	76	80
4	4-$MeOC_6H_4$	**6e**	75	60	72	58	79	78
5	2-$MeOC_6H_4$	**6f**	78	70	76	74	92	82
6	4-MeC_6H_4	**6h**	80	65	80	63	76	79
7	2- MeC_6H_4	**6i**	82	68	75	70	78	78
8	4-ClC_6H_4	**6k**	72	66	68	64	73	80
9	2-ClC_6H_4	**6l**	78	72	92	77	88	82
10	2-FC_6H_4	**6m**	80	69	78	67	84	78
11	1-Naphthyl	**6n**	72	70	65	68	92	75
12	2-Naphthyl	**6o**	75	68	63	66	80	77
13	$PhCH_2CH_2$	**6p**	78	65	76	63	65	78
14	2-Furfuryl	**6q**	80	67	78	65	72	80
15	Cyclohexyl	**6r**	74	66	72	65	65	74
16	^{n}Pr	**6s**	59	57	56	55	67	84
17	^{i}Pr	**6t**	54	60	47	58	63	86
18	^{n}Bu	**6u**	58	63	56	60	58	88
19	^{i}Bu	**6v**	54	65	57	64	53	90

[a] The reactions were carried out with 1 mmol of *p*-nitro benzaldehyde and 10 mmol of nitromethane in 2 mL of ^{i}PrOH in the presence of 10 mol % ligand and 5 mol % $Cu(OTf)_2$ at 0 °C.
[b] Values are isolated yields after chromatographic purification.
[c] Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column. The absolute configurations are determined by comparison of retention time (chiral HPLC) with the literature values.[10e,4k,l]
[d] The (*S*)-enantiomer was obtained.
[e] The (*R*)-enantiomer was obtained.

Table 6
Diastereoselective Henry reaction of various aldehydes with nitroethane[a]



5 *syn*-**7** *anti*-**7**

Entry	Aldehyde	Product	Yield[b] (%)	*syn*:*anti*[c]	ee[d] (%)	
					syn	*anti*
1	*p*-Nitrobenzaldehyde	**7a**	72	65:35	78	46
2	*p*-Methoxybenzaldehyde	**7b**	78	62:38	68	49
3	Isobutyraldehyde	**7c**	75	64:36	63	48
4	2-Methylbutyraldehyde	**7d**	74	61:39	68	52
5	Cyclohexanecarbaldehyde	**7e**	75	63:37	58	50
6	3-Phenylpropionaldehyde	**7f**	77	68:32	73	60

[a] All reactions were carried out with 1 mmol of *p*-nitro benzaldehyde and 10 mmol of nitromethane in 2 mL of ^{i}PrOH in the presence of 10 mol % ligand and 5 mol % $Cu(OTf)_2$ at 0 °C.
[b] Values are isolated yields after chromatographic purification.
[c] Diastereoselectivity was determined from ^{1}H NMR spectrum.
[d] Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column. The absolute configurations ere determined by comparison of retention time (chiral HPLC) with the literature values.[37g,l]

analysis. However, based on our experimental observations and the previously reported steric and electronic consideration,[10c,e,39] we propose two transition state models, which account for the absolute configuration of the products obtained ligands (4*S*,5*R*)-**3a** and (4*S*,5*R*)-**4a** (Fig. 1). According to the model proposed by Evans,[10e] in the favorable transition state, the nucleophilic carbon of the nitronate ion is formed in situ by deprotonation of nitromethane with a $[OTf]^{-}$ anion that approaches the aldehyde from the *Si* face to give the (*S*)-isomer as the major product. The *Re* face attack is not favored due to severe non-bonding interactions between the aromatic group, or aliphatic chain, of the corresponding aldehyde with the chiral ligands (4*S*,5*R*)-**3a** and (4*S*,5*R*)-**4a**.

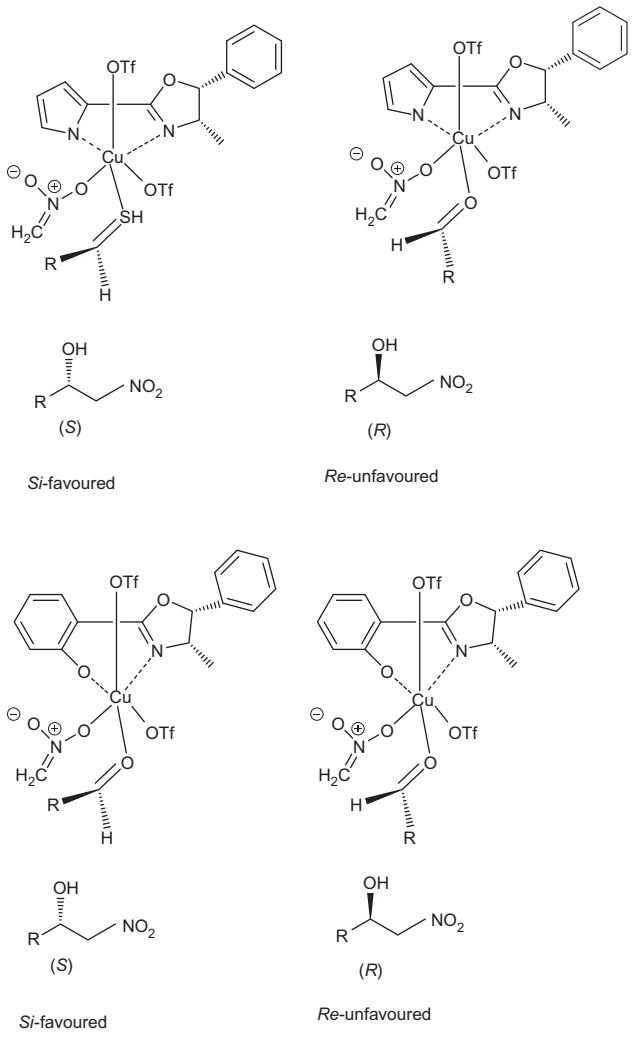


Figure 1. Proposed transition state models for the enantioselective Henry reaction.

3. Conclusion

In conclusion, we have synthesized novel chiral ligands from pyrrole-2-carbonitrile, salicylic acid, and norephedrine using two different methods and applied them as catalysts for enantioselective Henry reactions. The reactions proceeded smoothly to provide the corresponding adducts in good enantioselectivities for a wide range of substrates. The best result (86.0% ee) was obtained when the reactions were carried out with ligands where the free hydroxyl group had a phenyl ring. We determined the optimum conditions for the Henry reaction by using different Lewis acids, solvents, temperatures, and ligand ratios. The applications of these chiral oxazoline ligands in other asymmetric reactions are currently underway.

4. Experimental

4.1. General methods

Reagents and solvents were purchased from Aldrich, Merck and Fluka. All solvents were dried before use according to the standard procedures. All NMR spectra were recorded on a Bruker DPX-400 MHz spectrometer at room temperature. Chemical shifts (parts per million) are reported relative to TMS. Coupling constant are expressed as *J* values in Hertz. Thin layer chromatography (TLC) was performed using Merck Kieselgel 60 F254. Crude compounds were purified with column chromatography using silica gel (60–200 mesh except if stated different). All IR spectra were recorded on a 2000 Perkin–Elmer spectrometer. Optical rotations were recorded on a Autopol IV polarimeter. All melting points were measured with an Electrothermal melting point instrument. Elemental analyses were carried out on a LECO CHNS-932 series analyzer. Enantiomeric excesses were determined by HPLC analysis using a Shimadzu and Thermo Finnigan analyzer. All reactions were carried out under an N_2 atmosphere.

4.2. Synthesis of chiral oxazolines

4.2.1. Experimental procedure for the synthesis of pyrrole-2-carbonitrile 1

Pyrrole-2-carbaldehyde (10 mmol), NMP (15 mL), and $NH_2OH{\cdot}HCl$ (12 mmol) were refluxed at 110–115 °C. After cooling to room temperature, H_2O (50 mL) was added. The mixture was then extracted with ethyl acetate (3 × 20 mL), dried over $MgSO_4$, and filtered. After evaporation of the solvent, the crude product was purified by flash column chromatography (EtOAc/hexane, 1:6) to give compound **2** in 70% yield; bp: 92–94 °C; R_f: 0.70 (EtOAc/Hex, 1:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.18 (br s, 1H) 6.80 (br s,1H) 6.94 (br ss, 1H) 9,43 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 100.41, 110.29, 115.08, 120.64, 124.11.

4.2.2. Experimental procedure for the synthesis of chiral oxazoline ligands (4*S*,5*R*)-3a and (4*R*,5*S*)-3b

Ethylene glycol/glycerol (2:1) (30 mL), anhydrous K_2CO_3 (2.68 mmol), pyrrole-2-carbonitrile **2** (2.76 mmol), and norephedrine **2a**,**b** (2.71 mmol) were combined in a 100-mL round bottomed flask. The mixture was stirred at 120 °C for 24 h. After the reaction, it was cooled to room temperature, and ethyl acetate (30 mL) and brine (30 mL) were added, collection of the organic layer and water was carried out with ethyl acetate (3 × 30 mL). The combined organic phases were dried over $MgSO_4$ and filtered. After evaporation of the solvent the crude product was purified by flash column chromatography (EtOAc/hexane, 1:6).

4.2.2.1. (4*S*,5*R*)-4-Methyl-5-phenyl-2-(1*H*-pyrrol-2-yl)-4,5-dihydrooxazole (4*S*,5*R*)-3a. Yield (68%, 0.41 g): mp 108–110 °C; R_f: 0.20 (EtOAc/Hex, 1:3); $[\alpha]_D^{20} = -322$ (*c* 1.94, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.79 (d, *J* = 6.7 Hz, 3H) 4.56 (dq, *J* = 7.2 Hz, 1H, *J* = 6.8, 1H) 5.65 (d, *J* = 9.6 Hz, 1H) 6.22 (t, *J* = 3.2 Hz, 1H) 6.79 (dd, *J* = 3.6 Hz, *J* = 1.6 Hz, 1H) 6.87 (s, 1H) 7.17–7.25 (m, 2H) 7.26–7.32 (m, 3H) 10.03 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 17.95, 64.80, 83.93, 109.90, 113.11, 119.96, 122.21, 126.22, 127.95, 128.07, 128.34, 136.93, 158.01; IR (KBr) *v* 612, 1656, 2845, 3090, 3153; Anal. Calcd for $C_{14}H_{14}N_2O$: C 74.31, H 6.24, N 12.38, O 7.07; found: C 74.39, H 6.31, N 12.41, O 6.89.

4.2.2.2. (4*R*,5*S*)-4-Methyl-5-phenyl-2-(1*H*-pyrrol-2-yl)-4,5-dihydrooxazole (4*R*,5*S*)-3b. Yield (63%, 0.38 g): mp 109–111 °C; R_f: 0.20 (EtOAc/Hex, 1:3); $[\alpha]_D^{20} = +322$ (*c* 1.94, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.78 (d, *J* = 7.2 Hz, 3H) 4.53 (dq, *J* = 9.2 Hz, 1H, *J* = 6.8, 1H) 5.65 (d, *J* = 9.2 Hz, 1H) 6.22 (t, *J* = 3.6 Hz, 1H) 6.79 (dd, *J* = 3.6 Hz, *J* = 1.2 Hz, 1H) 6.88 (d, *J* = 1.2 Hz, 1H) 7.14 (m, 2H) 7.22–7.31 (m, 3H) 9.5 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 17.92, 64.77, 83.96, 109.96, 113.15, 119.93, 122.19, 126.22, 127.96, 128.34, 136.90, 157.95; IR (KBr) *v* 608, 1652, 2861, 3078, 3157.

4.2.3. Experimental procedure for the synthesis of chiral oxazoline ligands with carboxylic acid and amino alcohol (4*S*,5*R*)-4a and (4*R*,5*S*)-4b

Thionyl chloride/dichloromethane = 1:1 (2 mL) and salicylic acid (10 mmol) were stirred until gas production ceased. The solvent and excess of thionyl chloride were then removed under reduced pressure and 2-hydroxybenzoyl chloride was obtained. Under a nitrogen atmosphere, norephedrine (10 mmol) and Et_3N (40 mmol) were added to DCM (100 mL) and cooled to 0 °C. Next, 2-hydroxybenzoyl chloride (10 mmol) in DCM (10 mL) was added. The mixture was stirred at room temperature until reaction was complete. Next, MsCl (15 mmol) was added and stirred for 5 h after which NH_4Cl was added. Collection of the organic layer and water was carried out with DCM (3×30 mL). The combined organic phases were dried over $MgSO_4$ and filtered. After evaporation of the solvent, the crude product was purified by flash column chromatography (EtOAc/hexane, 1:6).

4.2.3.1. 2-((4*S*,5*R*)-4-Methyl-5-phenyl-4,5-dihydrooxazole-2-yl)phenol (4*S*,5*R*)-4a. Yield (68%, 1.72 g); $[\alpha]_D^{20} = +67.1$ (*c* 0.149, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.5 (d, *J* = 6.7 Hz, 3H) 4.28 (dq, *J* = 6.7 Hz, *J* = 6.7 Hz, 1H) 5.10 (d, *J* = 7.7 Hz, 1H) 6.90 (dt, *J* = 1.0 Hz, *J* = 7.6 Hz, 1H) 7.06 (m, 1H) 7.35–7.43 (m, 6H) 7.75 (m, 1H) 12.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 21.7, 69.9, 87.6, 110.9, 117.0, 118.9, 126.0, 128.4, 128.9, 129.2, 133.7, 139.9, 160.3, 164.5; IR ($CHCl_3$, Salt plate) *v* 1492, 1617, 1642, 2869, 2927, 2967, 3032, 3064; Anal. Calcd for $C_{16}H_{15}NO_2$: C 75.87, H 5.97, N 5.53, O 12.63; found: C 75.92, H 5.99, N 5.41, O 12.68.

4.2.3.2. 2-((4*R*,5*S*)-4-Methyl-5-phenyl-4,5-dihydrooxazole-2-yl)phenol (4*R*,5*S*)-4b. Yield (68%, 1.72 g); $[\alpha]_D^{20} = -67.1$ (*c* 0.149, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.6 (d, *J* = 6.7 Hz, 3H) 4.27 (dq, *J* = 6.7 Hz, *J* = 6.7 Hz, 1H) 5.10 (d, *J* = 7.7 Hz, 1H) 6.90 (m, 1H) 7.06 (m, 1H) 7.35–7.43 (m, 6H) 7.75 (m, 1H) 12.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 21.8, 70.1, 87.6, 110.7, 117.3, 119.1, 126.2, 128.4, 129.1, 129.4, 133.9, 140.2, 160.3, 164.7.

4.3. Asymmetric Henry reactions

4.3.1. Asymmetric Henry reaction in the presence of Et_2Zn

To a solution of chiral ligands (0.1 mmol) in dry toluene (2 mL) at 0 °C under a nitrogen atmosphere was added a solution of diethylzinc (3 mL, 1.0 M in hexane) via syringe. After stirring for 15 m at 0 °C, CH_3NO_2 (10 mmol) and *p*-nitrobenzaldehyde (1 mmol) were added. The reaction mixture was stirred at 0 °C and monitored by TLC. When the reaction was finished, NH_4Cl was added at −15 °C. When the mixture's temperature reached room temperature, the mixture was extracted with chloroform (3×10 mL), dried over $MgSO_4$, and filtered. After evaporation of the solvent, the crude product was purified by flash column chromatography (EtOAc/hexane, 1:6).

4.3.2. Asymmetric Henry reaction in the presence of $Cu(OAc)_2 \cdot H_2O$

Under an nitrogen atmosphere, the chiral ligand (0.1 mmol) and $Cu(OAc)_2 \cdot H_2O$ (0.1 mmol) in the solvent (2 mL) was stirred for 1 h at room temperature. Next, CH_3NO_2 (10 mmol) and substituted benzaldehyde (1 mmol) were added. When the reaction was complete, the solvent was removed under reduced pressure and the mixture was extracted with chloroform (3×10 mL), dried over $MgSO_4$, and filtered. After evaporation of the solvent, the crude product was purified by flash column chromatography (EtOAc/hexane, 1:6). The adducts were fully characterized by comparison of their spectroscopic data with those reported in the literature. The diastereoselectivity was determined from the ^1H NMR spectrum. The enantiomeric purity of the product was determined by HPLC analysis. The absolute configuration of the products was assigned by comparison to the literature data.[11a,33a,d,38g–l]

4.3.2.1. (*S*)-2-Nitro-1-(4-nitrophenyl)ethanol 6a. For the Chiralcel OD-H column, solvent: *n*-hexane/^{i}PrOH (85:15), flow rate: 1.0 mL/min, UV 215 nm, retention times: major enantiomer (*S*) t_r 28.21 min, minor enantiomer (*R*) t_R: 18.80 min for (*R*).

4.3.2.2. (*S*)-2-Nitro-1-(2-nitrophenyl)ethanol 6b. For the Chiralcel OD-H column, solvent: *n*-hexane/^{i}PrOH (90:10), flow rate: 0.8 mL/min, UV 215 nm, retention times: major enantiomer (*S*) t_r 26.40 min, minor enantiomer (*R*) t_R: 20.25 min for (*R*).

4.3.2.3. (*S*)-1-Phenyl-2-nitroethanol 6c. For the Chiralcel OD-H column, solvent: *n*-hexane/^{i}PrOH, (90:10), flow rate: 0.6 mL/min, UV 215 nm, retention times: major enantiomer (*S*) t_r: 18.41 min, minor enantiomer (*R*) t_R: 15.47 min.

4.3.2.4. (*S*)-1-(4-Methoxyphenyl)-2-nitroethanol 6d. For the Chiralcel OD-H column, solvent: *n*-hexane/^{i}PrOH, (90:10), flow rate. 0.8 mL/min, UV 215 nm retention times: major enantiomer (*S*) t_r: 16.20 min, minor enantiomer (*R*) t_r: 13.7 min.

4.3.2.5. (*S*)-1-(2-Methoxyphenyl)-2-nitroethanol 6e. For the Chiralcel OD-H column, solvent: *n*-hexane/^{i}PrOH (90:10), flow rate: 0.8 mL/min, UV 215 nm, retention times: major enantiomer (*S*) t_r: 24.29 min, minor enantiomer (*R*) t_r: 23.43 min.

4.3.2.6. (*S*)-1-(4-Methylphenyl)-2-nitroethanol 6f. For the Chiralcel OD-H column, solvent: *n*-hexane/^{i}PrOH, (90:10), flow rate. 0.5 mL/min, UV 215, retention times: major enantiomer (*S*) t_r: 32.00 min, minor enantiomer (*R*) t_r: 27.10 min.

4.3.2.7. (*S*)-1-(2-Methylphenyl)-2-nitroethanol 6g. For the Chiralcel OD-H column, solvent: *n*-hexane/^{i}PrOH (90:10), flow rate: 0.5 mL/min, UV 215 nm, retention times: major enantiomer (*S*) t_r: 30.12 min, minor enantiomer (*R*) t_r: 22.50 min.

4.3.2.8. (*S*)-1-(4-Chlorophenyl)-2-nitroethanol 6h. For the Chiralcel AD-H column, solvent: *n*-hexane/^{i}PrOH (90:10), flow rate: 0.8 mL/min, UV 215 nm, retention times: major enantiomer (*S*) t_r: 26.29 min, minor enantiomer (*R*) t_r: 22.50 min.

4.3.2.9. (*S*)-1-(2-Chlorophenyl)-2-nitroethanol 6i. For the Chiralcel OJ-H column, solvent: *n*-hexane/^{i}PrOH (97:3), flow rate: 0.8 mL/min, UV 215 nm, retention times: major enantiomer (*S*) t_r: 29.25 min, minor enantiomer (*R*) t_r: 23.44 min.

4.3.2.10. (*S*)-1-(4-Fluorophenyl)-2-nitroethanol 6j. For the Chiralcel OB-H column, solvent: *n*-hexane/^{i}PrOH (90:10), flow rate. 0.8 mL/min, UV 215 nm, retention times: major enantiomer (*S*) t_r: 12.60 min, minor enantiomer (*R*) t_r: 11.50 min.

4.3.2.11. (*S*)-1-(4-Trifluoromethyl)phenyl)-2-nitroethanol 6k. For the Chiralcel OD-H column, solvent: n-hexane/^{i}PrOH (85:15), flow rate: 0.8 mL/min, UV 215 nm, retention times: major enantiomer (*S*) t_r: 15.67 min, minor enantiomer (*R*) t_r: 12.45 min.

4.3.2.12. (*S*)-1-(1-Naphthyl)-2-nitroethanol 6l. For the Chiralcel OD-H column, solvent: *n*-hexane/^{i}PrOH (85:15), flow rate: 0.8 mL/min, UV 215 nm, retention times: major enantiomer (*S*) t_r: 28.30 min, minor enantiomer (*R*) t_r: 23.45 min.

4.3.2.13. (*S*)-1-(2-Naphthyl)-2-nitroethanol 6m. For the Chiralcel AD-H column, solvent: *n*-hexane/^{i}PrOH (85:15), flow rate:

0.8 mL/min, UV 215 nm, retention times: major enantiomer (*S*) t_r: 23.30 min, minor enantiomer (*R*) t_R: 18.00 min.

4.3.2.14. (*S*)-1-(2-Furyl)-2-nitroethanol 6n. For the Chiralcel AD-H column, solvent: *n*-hexane/^{i}PrOH, (85:15), flow rate: 0.8 mL/min, UV 215 nm, retention times: major enantiomer (*S*) t_r: 24.22 min, minor enantiomer (*R*) t_r: 18.40 min.

4.3.2.15. (*S*)-1-Cyclohexyl-2-nitroethanol 6o. For the Chiralpak AD-H column, solvent: *n*-hexane-^{i}PrOH (97:3), flow rate: 0.8 mL/min, UV 215 nm,. retention times: major enantiomer (*S*) t_r: 22.15 min, minor enantiomer (*R*) t_R: 24.50 min.

4.3.2.16. (*S*)-1-Nitropentan-2-ol 6p. For the Chiralpak AD-H column, solvent: *n*-hexane-^{i}PrOH (98:2), flow rate: 1 mL/min, UV 215 nm, retention times: major enantiomer (*S*) t_r: 45.30 min, minor enantiomer (*R*) t_r: 34.30 min.

4.3.2.17. (*S*)-3-Methyl-1-nitrobutan-2-ol 6r[11a,33a]. For the Chiralcel OD-H column, solvent: *n*-hexane/^{i}PrOH (97:3), flow rate: 0.6 mL/min, UV 220 nm, retention times: major enantiomer (*S*) t_r: 31.20 min, minor enantiomer (*R*) t_r: 27.90 min.

4.3.2.18. (*S*)-1-Nitrohexan-2-ol 6s. For the Chiralcel AD–H column, solvent: hexane/^{i}PrOH (98:2), flow rate: 0.8 mL/min, UV 215 nm, retention times: major enantiomer (*S*) t_r: 37.60 min, minor enantiomer (*R*) t_r: 28.75 min.

4.3.2.19. (*S*)-4-Methyl-1-nitropentan-2-ol 6t. For the Chiralcel OJ-H column, solvent: *n*-hexane/^{i}PrOH (98:2), flow rate: 0.6 mL/min, UV 215 nm, retention times: major enantiomer (*S*) t_r: 41.70 min, minor enantiomer (*R*) t_r: 36.20 min.

4.3.2.20. (1*S*,2*S*)-1-(4-Nitrophenyl)-2-nitropropan-1-ol 7a. For the Chiralcel OD-H and Chiralpak AD-H column, solvent: hexane/^{i}PrOH (80:20), flow rate: 1.0 mL/min, UV 210 nm, retention times: syn_{major} (1*S*,2*S*) t_r = 24.81 min, syn_{minor} (1*R*,2*R*) t_r = 21.60 min. Diastereomeric ratio (*syn*/*anti*) was determined by ^{1}H NMR. The absolute configuration of both diastereomers was assigned by comparison of the retention time in HPLC with the literature data.[1b,33,38g–j] ^{1}H NMR spectroscopic data were in agreement with the literature values.[38k,38l]

4.3.2.21. (1*S*,2*S*)-1-(4-Methoxyphenyl)-2-nitropropan-1-ol 7b. For the Chiralpak AD-H column, solvent: hexane/^{i}PrOH (90:10), flow rate: 1.0 mL/min, UV 215 nm, retention times:, syn_{major} (1*S*,2*S*) t_r:20.00 min, syn_{minor} (1*R*,2*R*) t_r:18.10 min. Diastereomeric ratio (*syn*/*anti*) was determined by ^{1}H NMR. The absolute configuration of both diastereomers was assigned by comparison of the retention time in HPLC with the literature data.[38g–j] ^{1}H NMR spectroscopic data were in agreement with the literature values.[38k,l]

4.3.2.22. (3*S*,4*S*)-2-Methyl-4-nitropentan-3-ol 7c. For the Chiralcel OD-H column, solvent (hexane/^{i}PrOH (99:1), flow rate: 0.8 mL/min, UV 220 nm, retention times: syn_{major} (1*S*,2*S*) t_r: 20.20 min, syn_{minor} (1*R*,2*R*) t_r:17.30 min. The absolute configuration of both diastereomers was assigned by comparison of the retention time in HPLC with the literature data. Diastereomeric ratio (*syn*/*anti*) was determined by ^{1}H NMR. The absolute configuration of both diastereomers was assigned by comparison of the retention time in HPLC with the literature data.[38g–j] ^{1}H NMR spectroscopic data were in agreement with the literature.

4.3.2.23. (2*S*,3*S*)-5-Methyl-2-nitrohexan-3-ol 7d. For the Chiralcel AD-H column, solvent hexane/^{i}PrOH (97:3), flow rate: 0.8 mL/min, UV 220 nm, retention time: syn_{major} (1*S*,2*S*) t_r: 19.70 min, syn_{minor} (1*R*,2*R*) t_r:15.45 min. Diastereomeric ratio (*syn*/*anti*) was determined by ^{1}H NMR. The absolute configuration of both diastereomers was assigned by comparison of the retention time in HPLC with the literature data.[38g–j] ^{1}H NMR spectroscopic data were in agreement with the literature.

4.3.2.24. (1*S*,2*S*)-1-Cyclohexyl-2-nitropropan-1-ol 7e. For the Chiralcel AD-H column, solvent: hexane/^{i}PrOH (95:5), flow rate: 0.8 mL/min, UV 225 nm, retention times: syn_{major} (1*S*,2*S*) t_r: 18.50 min, syn_{minor} (1*R*,2*R*) t_r: 15.70 min. Diastereomeric ratio (*syn*/*anti*) was determined by ^{1}H NMR. The absolute configuration of both diastereomers was assigned by comparison of the retention time in HPLC with the literature data.[38g–j] ^{1}H NMR spectroscopic data were in agreement with the literature values.

4.3.2.25. (3*S*,4*S*)-4-Nitro-1-phenylpentan-3-ol 7f. For the Chiralcel AD-H column, solvent: hexane/^{i}PrOH (95:5), flow rate: 1.0 mL/min, 210 nm, retention times: syn_{major} (1*S*,2*S*) t_r: 26.20 min, syn_{minor} (1*R*,2*R*) t_r: 18.45 min. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (hexane/isopropanol = 96:4, 1.0 mL/min, 220 nm), for *syn*-product, t_{major} = 18.7 min, t_{minor} = 17.3 min. Diastereomeric ratio (*syn*/*anti*) was determined by ^{1}H NMR. The absolute configuration of both diastereomers was assigned by comparison of the retention time in HPLC with the literature data.[38g–j] ^{1}H NMR spectroscopic data were in agreement with the literature values.[38k,l]

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