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A study of chiral oxazoline ligands with a 1,2,4-triazine and other six-membered aza-heteroaromatic rings and their application in Cu-catalysed asymmetric nitroaldol reactions

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ABSTRACT

Enantiomerically pure oxazoline ligands with variously substituted 1,2,4-triazine rings have been synthesized using the Pd-catalysed cross-coupling amination of 3-halo-1,2,4-triazines. The catalytic efficiency of the ligands was studied in the asymmetric Henry reaction of nitromethane with several aldehydes. The appropriate β-nitro alcohols were formed in good yields (up to 93%) and with up to 78% ee. The impact of the substitution of the 1,2,4-triazine ring on the nitroaldol reaction is discussed. In order to investigate the influence of the 1,2,4-triazine ring on the catalytic activity of the ligands, ligands where the 1,2,4-triazine ring was replaced by a pyridine, pyrimidine, pyrazine or pyridine *N*-oxide ring were synthesized and applied to asymmetric nitroaldol reactions.

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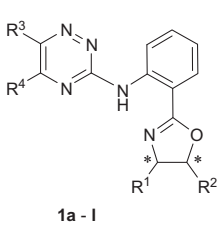
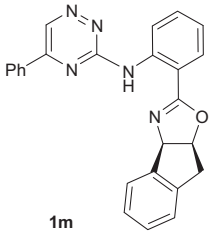
1. Introduction

Metal-based asymmetric catalysis[1] constitutes a large research area, and the field is still being rapidly developed along with an expansion of organocatalysis.[2] Since the selectivity of metal catalysts is largely determined by the ligands, ligand design is a major topic in asymmetric catalysis. In 1986, Brunner first described the use of chiral oxazoline (4,5-dihydrooxazole) based ligands in the asymmetric monophenylation of *cis*-cyclohexan-1,2-diol and *meso*-butan-2,3-diol.[3] Since then such ligands have been found to be very active in numerous metal-catalysed enantioselective processes.[4] The structures of the oxazoline ligands differ depending on the number of oxazoline rings, additional chiral elements and specific structural features. Among them, C_2-symmetric bis(oxazolines) are one of the most popular classes of chiral ligands and have been extensively studied by many research groups.[4c,e] In contrast, monooxazoline ligands, although represented by a large number of various structures, are much less explored. Many additional heteroatom donors such as nitrogen, oxygen, sulfur and phosphorus are incorporated into different structures of the oxazoline ligands thus forming many mono-, bi- and tridentate ligands.[4] The additional electron donor can be derived either from a functional group or heterocyclic ring.

In line with our interests in 1,2,4-triazine-oxazoline ligands, we have reported on novel ligands **1** bearing a 1,2,4-triazine ring, an NH group and a chiral oxazoline moiety (Fig. 1).[5]



1a - l



1m

a: $R^3 = R^4 = Ph$, $R^2 = H$, $R^1 = t\text{-Bu}$ (*S*)
b: $R^3 = R^4 = Ph$, $R^2 = H$, $R^1 = Ph$ (*S*)
c: $R^3 = R^4 = Ph$, $R^2 = H$, $R^1 = i\text{-Pr}$ (*S*)
d: $R^3 = R^4 = Ph$, $R^2 = H$, $R^1 = Bn$ (*R*)
e: $R^3 = H$, $R^4 = Ph$, $R^2 = H$, $R^1 = t\text{-Bu}$ (*S*)
f: $R^3 = H$, $R^4 = Ph$, $R^2 = H$, $R^1 = Ph$ (*S*)
g: $R^3 = H$, $R^4 = Ph$, $R^2 = H$, $R^1 = i\text{-Pr}$ (*S*)
h: $R^3 = H$, $R^4 = t\text{-Bu}$, $R^2 = H$, $R^1 = t\text{-Bu}$ (*S*)
i: $R^3 = H$, $R^4 = t\text{-Bu}$, $R^2 = H$, $R^1 = Ph$ (*S*)
j: $R^3 = H$, $R^4 = t\text{-Bu}$, $R^2 = H$, $R^1 = i\text{-Pr}$ (*S*)
k: $R^3 = H$, $R^4 = t\text{-Bu}$, $R^2 = H$, $R^1 = Bn$ (*R*)
l: $R^3 = H$, $R^4 = R^2 = R^1 = Ph$ (4*R*, 5*S*)

Figure 1. Previous work: 1,2,4-triazine-oxazoline ligands with a flexible substituent in the oxazoline ring and with an indane moiety.

Ligands with two differentiated sp^2-hybridized coordinating nitrogen atoms have found wide application in enantioselective metal-catalysed reactions[6] and may also serve as ligands able to form bifunctional catalysts with metals.[7] Thus, the structures of ligands **1** have been designed on the assumption that (1) both the nitrogen atoms of the 1,2,4-triazine moiety and the oxazoline

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nitrogen atom would be responsible for coordination to a metal ion, together with the NH group; and (2) the 1,2,4-triazine nitrogen atom can act as a Lewis base in the complexes formed by these ligands. Ligands **1** were found to be active stereocontrollers in Cu-catalysed asymmetric nitroaldol reactions of a series of aromatic and aliphatic aldehydes, providing the products with enantioselectivities of up to 92%.[5] The enantiomeric excesses thus obtained were due to the substitution pattern in the oxazoline ring, while the substituents in the 1,2,4-triazine ring of ligands **1a–l** affect the solubility of the ligands or their Cu-complexes have an impact on the course of the asymmetric reaction. Ligands **1a–d** with two phenyl substituents in the 1,2,4-triazine ring afforded Henry adducts in lower yields than their counterparts with one phenyl ring at the 5-position of the 1,2,4-triazine. This observation prompted us to design ligands **2** and **3** with a 1,2,4-triazine having a phenyl ring at the 6-position and an unoccupied 5-position. In order to further investigate the influence of the substitution in the 1,2,4-triazine ring on ligand activity we also prepared ligand **4** characterized by the presence of a phenanthro-fused 1,2,4-triazine unit (Fig. 2). The phenanthrene moiety prevents free rotation of the phenyl at the 5-position and provides its coplanar arrangement with the triazine ring in comparison to ligands **1**,[8] which may affect the geometry of the active complex.

Herein we report the synthesis of ligands **2**, **3** and **4** and their application in enantioselective Henry reactions. Since the actual contribution of a 1,2,4-triazine ring to the activity of the 1,2,4-triazine-oxazoline ligands is not clearly defined, several analogous ligands with pyridine **5a**, **6a**, pyrimidine **5b**, **6b**, **7**, **8** and pyrazine **5c**, **6c** instead of a 1,2,4-triazine ring were also synthesized and tested in the asymmetric nitroaldol reaction for comparison studies (Fig. 3). It is well documented that amine *N*-oxides act as powerful electron-pair donors and that the introduction of such a group into the ligand structure provides suitable electronic environments for a central metal ion.[9] Unfortunately, the number of ligands combining a pyridine *N*-oxide and oxazoline in the molecule is very limited. A detailed search allowed us to find only two papers devoted to this type of ligand. Ma and Andrus have reported on the synthesis and application of oxazoline-pyridine *N*-oxide ligands in the asymmetric allylation of aldehydes with allylchlorosilanes.[10a] Another ligand was synthesized by Reiser, but there is no information on its application in asymmetric catalysis.[10b] This area remains very attractive for development, thus oxazoline ligands **5e–f** with a pyridine *N*-oxide moiety were also synthesized and used in the asymmetric Henry reaction (Fig. 3).

2. Results and discussion

2.1. Synthesis of ligands

Ligands **2**, **3** and **4** were prepared based on the synthetic strategy outlined in Scheme 1. Initially, appropriate 2-(*o*-aminophenyl)oxazolines **12a–b** and **13** were obtained by condensation of enantiomerically pure aminoalcohols **10a–b** and **11** with the CN group of 2-aminobenzonitrile **9** in the presence of a threefold excess of $ZnCl_2$ in chlorobenzene at reflux over 24 h.[11] Subsequently, the Buchwald-Hartwig amination[12] of 3-chloro-1,2,4-triazines **14a** and **14b** with 2-(*o*-aminophenyl)oxazolines **12a–b** and **13** was conducted to furnish the desired chiral ligands **2a–b**, **3** and **4**. The conditions of the reaction, in terms of the amount of palladium source and ligand were elaborated by us previously.[5a] Thus the Buchwald–Hartwig reactions were carried out in boiling dioxane using Pd_2dba_3 (10 mol %) as the palladium source, Xantphos (20 mol %) as the ligand and K_2CO_3 as the base.

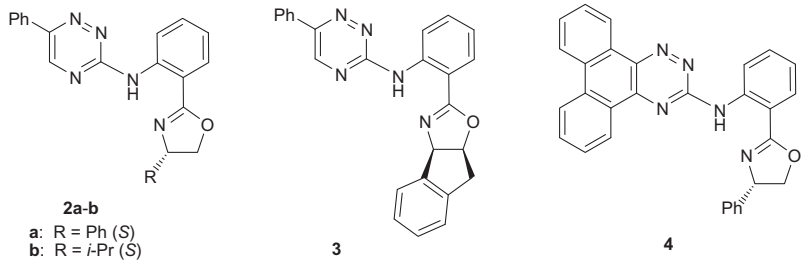


Figure 2. New 1,2,4-triazine oxazoline chiral ligands.

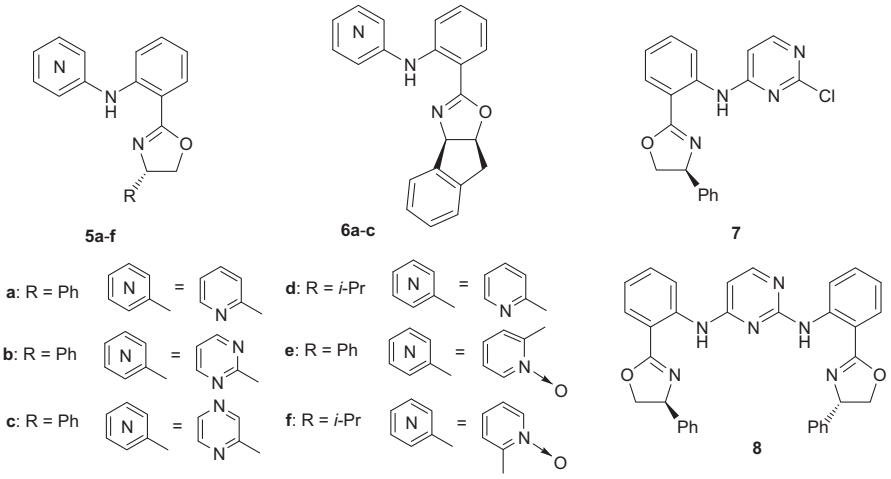
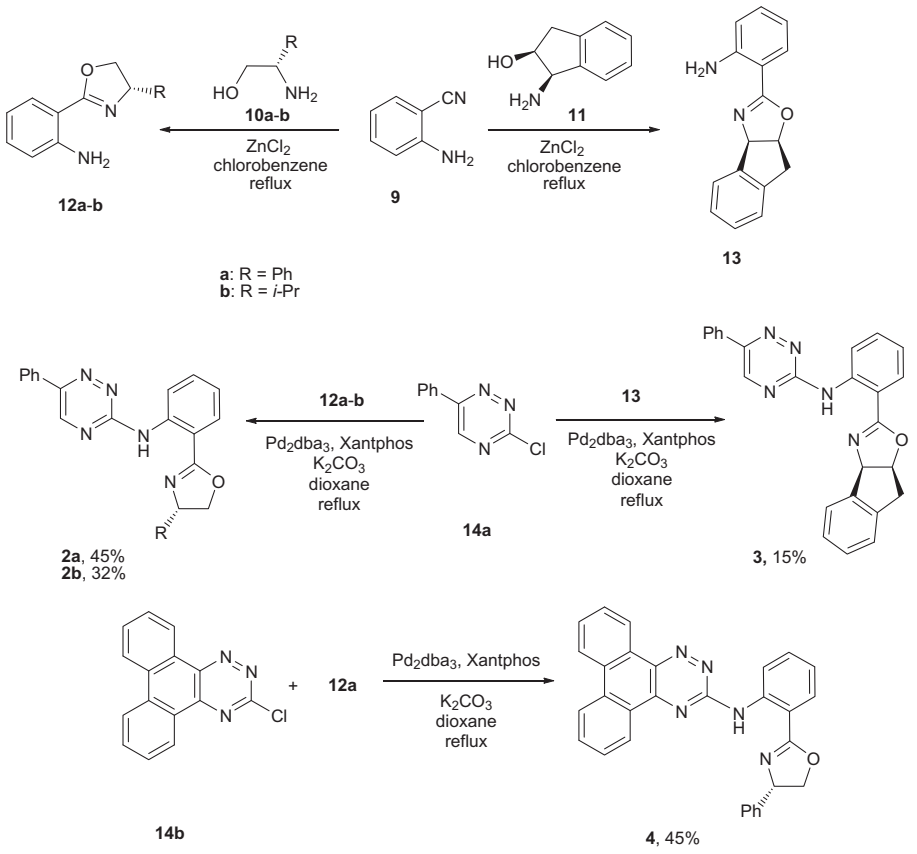


Figure 3. Chiral oxazoline ligands with pyridine, pyrimidine, pyrazine and pyridine *N*-oxide rings.



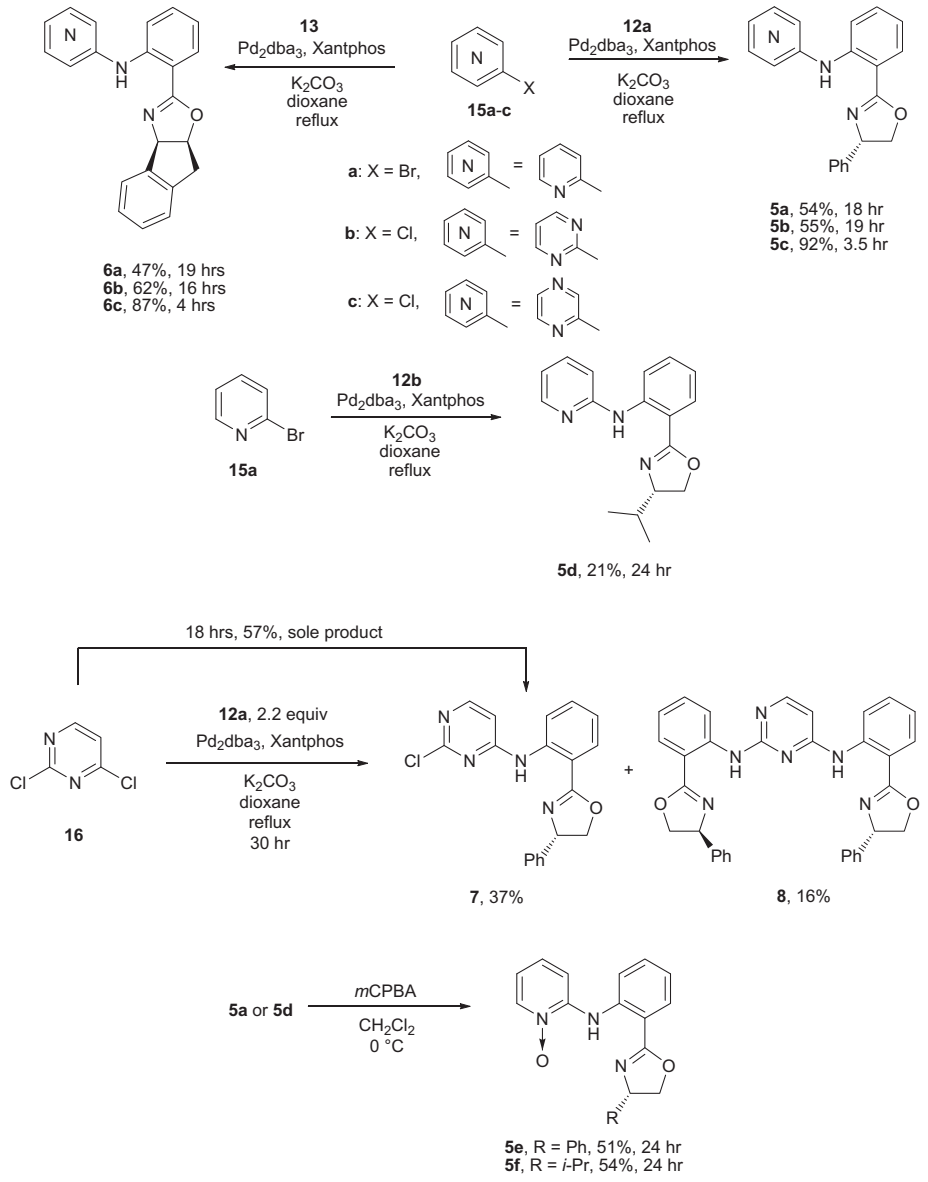
Scheme 1. Synthesis of ligands **2a**–**b**, **3** and **4**.

The Pd-catalysed C–N bond formation was also a key step in the synthesis of ligands with a pyridine, pyrimidine or pyrazine ring (Scheme 2). Compounds **5a** and **5d** have already been synthesized from 2-bromopyridine by Guiry using a palladium catalysed aryl amination. After 1 h of microwave irradiation, the compounds were isolated in 60% and 83% yields.[13] In our case, ligands **5a** and **5d** were formed in 54% and 21% yields, respectively, from 2-bromopyridine **15a** and 2-(*o*-aminophenyl)oxazolines **12a**–**b** upon conventional heating at 108 °C. Heating for 19 h was necessary to obtain ligand **5b** in 55% yield. The Buchwald–Hartwig aminations of 2-chloropyrazine **15c** with **12a** were completed after 3.5 h to give ligand **5c** in a yield of 92%. In an analogous manner, ligands **6a**–**c** with an indanol-derived substituent in the oxazoline ring were prepared. Continued efforts were directed towards the synthesis of C_1-symmetrical bisoxazoline ligand **8** derived from 2,4-dichlopyrimidine **16**. Amination of 2,4-dichloropyrimidine **16** with 2.2 equiv of 2-(*o*-aminophenyl)oxazoline **12a** after 18 h of heating in boiling dioxane resulted in the formation of monosubstituted product **7** in 57% yield. When the reaction time was prolonged to 30 h, ligand **8** was obtained in 16% yield in addition to compound **7** being isolated in a yield of 37%. Further extension of the time or the addition of a larger amount of catalyst did not increase the yield of the desired ligand **8**. Ligands **5e** and **5f** with an *N*-oxide function in the pyridine ring were synthesized by the oxidation of **5a** and **5d** with *m*-chloroperbenzoic acid (Scheme 2). We decided to conduct the oxidation process at a low temperature in order to avoid any oxidation of the oxazoline ring.[14] However, when the reaction was carried out at −20 °C in dichloromethane the products did not form. We found that 0 °C was the optimal temperature for the oxidation reaction. Thus, *N*-oxides **5e** and **5f** were obtained in yields of 51 and 54%, respectively.

2.2. Enantioselective Henry reactions

For a preliminary study, ligands with the 1,2,4-triazine ring were applied as catalysts in the asymmetric nitroaldol reaction, in which *m*-nitrobenzaldehyde and nitromethane were used as model substrates. The results of the reactions carried out in the presence of 5 mol % of $Cu(OAc)_2 \cdot H_2O$ in different solvent systems are shown in Table 1.

In 2-propanol, the highest yield was observed in reactions carried out in the presence of ligands **2a** and **2b** (Table 1, entries 1 and 2). Unfortunately the enantiomeric purity of the products obtained was low. Ligands **3** and **4** were found to be strongly insoluble in 2-propanol which affected their efficiency in the reaction (Table 1, entries 3 and 6). Changing the solvent to THF improved the chemical yield of both ligands, especially for ligand **4**, but it had a negative effect on the enantioselectivity (Table 1, entries 4 and 7). In the reaction catalysed by **3**, a racemic product was obtained in THF. A 2-propanol/THF (1:1) solvent system did not increase the reaction yield in which ligand **3** was used as a catalyst; however the enantioselectivity increased to 17% (Table 1, entry 5). This was the best result that we managed to obtain for ligand **3**. Therefore, we turned our attention to ligand **4** since we were interested in determining the influence of the phenanthrene unit on the properties of ligands. The reaction conducted in the presence of the ligand in a 2:1 mixture of 2-propanol/THF yielded the product at 73% conversion and 37% ee (Table 1 entry 8). A reversal in the ratio of the reaction medium components (2-propanol/THF, 1:2) allowed us to obtain the product in a better yield of 87%, while the enantiomeric purity remained almost the same (Table 1 entry 10). A significant improvement of the yield and enantioselectivity was achieved when a mixture of 2-propanol/THF in a ratio of 1:1



Scheme 2. Synthesis of ligands with a pyridine, pyrimidine, pyrazine or pyridine *N*-oxide ring.

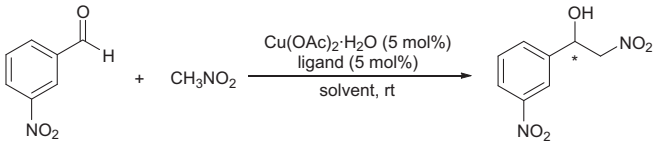
was applied as the solvent. Under these conditions, the reaction proceeded in 92% yield and with an enantioselectivity of 41% (Table 1, entry 9).

Having obtained the optimal solvent conditions, we decided to check the scope of the reaction. For these studies, ligands **2a** and **4** were chosen due to the different substitution pattern in the 1,2,4-triazine ring. The results of the asymmetric addition of nitromethane to a series of aldehydes in the presence of ligands **2a** and **4** are collected in Table 2.

Analysing the results obtained by using ligand **2a**, it can be seen that the enantioselectivity varied in the range of 18 to 78% (Table 2, entries 1–16). The yield of the products significantly depends on the nature of the aldehydes. Benzaldehydes with electron-withdrawing groups in the phenyl ring reacted faster (Table 2, entries 1 and 3–8) than aldehydes substituted with electron-donating ones (Table 2, entries 9–15). However, the electronic nature of the substituents does not have an influence on the enantioselectivity. The reaction of an aliphatic aldehyde, hydrocinnamaldehyde **17p** afforded the product with enantioselectivity of 50% and a low yield (Table 2, entry 16). In some cases, precipitation of a **2a**-Cu complex was observed. Unfortunately isolation of the complex and preparation of a crystal suitable for X-ray analysis were not successful. When ligand **4** was used as the catalyst, the nitroaldol reactions proceeded with better enantioselectivities and higher yields (Table 2, entries 17–21). In the reactions tested (*S*)-enriched β-nitro alcohols were produced, with the exception of the reaction of 4-chlorobenzaldehyde **17g** catalysed by **2a**, when the formation of the (*R*)-enantiomer of **19g** was favoured (Table 2, entry 7). Conversely, in the reaction of 4-chlorobenzaldehyde conducted in the presence of ligand **4**, the (*S*)-enantiomer was formed predominantly (Table 2, entry 20). Both ligands **2a** and **4** possess an (*S*)-configured stereocenter at the 4-position of the oxazoline ring; therefore the stereodifferentiation in the reaction may be due to the substitution in the 1,2,4-triazine ring. It is worth noting that our previously described (*R*)-configured ligands **1l** and **1m** with a phenyl substituent at the 5-position of the 1,2,4-triazine initiated the formation of an (*R*)-enriched product in the reaction of 4-chlorobenzaldehyde.[5b]

In subsequent studies, we undertook efforts to examine the role of the 1,2,4-triazine moiety on the catalytic efficiency of our triazine-oxazoline ligands. Comparison experiments involving ligands **5a–c**, **5e–f**, **6a–c**, **7**, and **8**, where the 1,2,4-triazine ring is

Table 1
Screening of ligands **2a–b**, **3** and **4**[a]



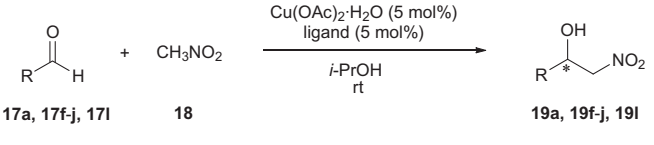
17a **18** **19a**

	Ligand	Solvent	Yield[b] (%)	ee[c] (%)
1	**2a**	*i*-PrOH	88	18 (*S*)
2	**2b**	*i*-PrOH	77	14 (*S*)
3	**3**	*i*-PrOH	51	4 (*R*)
4	**3**	THF	68	*rac*
5	**3**	*i*-PrOH/THF (1:1)	68	17 (*S*)
6	**4**	*i*-PrOH	38	32 (*S*)
7	**4**	THF	85	13 (*S*)
8	**4**	*i*-PrOH/THF (2:1)	73	37 (*S*)
9	**4**	*i*-PrOH/THF (1:1)	92	41 (*S*)
10	**4**	*i*-PrOH/THF (1:2)	87	36 (*S*)

[a] All reactions were performed on a 0.5 mmol scale with 5 mol % of ligand and 5 mol % of $Cu(OAc)_2·H_2O$ at room temperature for 98 h.
[b] Yields of isolated products.
[c] Enantiomeric excess was determined by HPLC using Chiracel OD-H column. The absolute configuration was assigned by comparing their specific rotations or the HPLC elution order with data from the literature.

replaced by a pyridine, pyrimidine, pyrazine or pyridine *N*-oxide ring were conducted. The results of the asymmetric addition of nitromethane to several aldehydes are presented in Table 3.

Table 3
Screening of ligands **5a–c**, **5e–f**, **6a–c**, **7** and **8**[a]

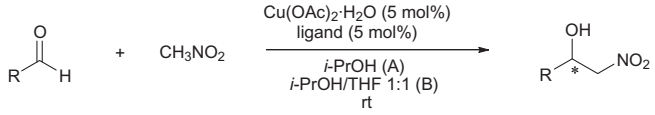


17a, 17f-j, 17l **18** **19a, 19f-j, 19l**

	R	Aldehyde	Ligand	Product	Yield[b] (%)	ee[c] (%)
1	3-$NO_2C_6H_4$	**17a**	**5a**	**19a**	37	4 (*S*)
2	3-$NO_2C_6H_4$	**17a**	**5b**	**19a**	63	11 (*S*)
3	3-$NO_2C_6H_4$	**17a**	**5c**	**19a**	57	8 (*S*)
4	3-$NO_2C_6H_4$	**17a**	**6a**	**19a**	80	23 (*S*)
5	3-$NO_2C_6H_4$	**17a**	**6b**	**19a**	71	29 (*S*)
6	3-$NO_2C_6H_4$	**17a**	**6c**	**19a**	58	11 (*S*)
7	3-$NO_2C_6H_4$	**17a**	**7**	**19a**	65	*rac*
8	3-$NO_2C_6H_4$	**17a**	**8**	**19a**	87	12 (*S*)
9	4-ClC_6H_4	**17g**	**5a**	**19g**	15	23 (*S*)
10	3-ClC_6H_4	**17f**	**5b**	**19f**	35	34 (*S*)
11	3-MeC_6H_4	**17j**	**5b**	**19j**	9	17 (*S*)
12	2-$MeOC_6H_4$	**17l**	**5b**	**19l**	39	34 (*S*)
13	2-BrC_6H_4	**17h**	**6a**	**19h**	44	64 (*R*)
14	2-MeC_6H_4	**17i**	**6a**	**19i**	22	63 (*R*)
15	2-BrC_6H_4	**17h**	**6b**	**19h**	22	67 (*R*)
16	3-$NO_2C_6H_4$	**17a**	**5e**	**19a**	81	14 (*S*)
17	3-$NO_2C_6H_4$	**17a**	**5f**	**19a**	88	11 (*S*)

[a] All reactions were performed on a 0.5 mmol scale with 5 mol % of ligand and 5 mol % of $Cu(OAc)_2·H_2O$ in 2-propanol at room temperature for 98 h.
[b] Yields of isolated products.
[c] Enantiomeric excess was determined by HPLC using Chiracel OD-H column. The absolute configuration was assigned by comparing their specific rotations or the HPLC elution order with data from the literature.

Table 2
Scope of aldehydes in the catalytic enantioselective Henry reaction[a]



17a-p **18** **19a-p**

	R	Aldehyde	Ligand	Solvent	Product	Yield[b] (%)	ee[c] (%)
1	3-$NO_2C_6H_4$	**17a**	**2a**	A	**19a**	88	18 (*S*)
2	Ph	**17b**	**2a**	A	**19b**	35	30 (*S*)
3	2-$NO_2C_6H_4$	**17c**	**2a**	A	**19c**	85	43 (*S*)
4	4-$NO_2C_6H_4$	**17d**	**2a**	A	**19d**	93	23 (*S*)
5	2-ClC_6H_4	**17e**	**2a**	A	**19e**	63	55 (*S*)
6	3-ClC_6H_4	**17f**	**2a**	A	**19f**	41	29 (*S*)
7	4-ClC_6H_4	**17g**	**2a**	A	**19g**	48	78 (*R*)
8	2-BrC_6H_4	**17h**	**2a**	A	**19h**	70	68 (*S*)
9	2-MeC_6H_4	**17i**	**2a**	A	**19i**	45	39 (*S*)
10	3-MeC_6H_4	**17j**	**2a**	A	**19j**	20	38 (*S*)
11	4-MeC_6H_4	**17k**	**2a**	A	**19k**	Traces	—
12	2-$MeOC_6H_4$	**17l**	**2a**	A	**19l**	16	56 (*S*)
13	3-$MeOC_6H_4$	**17m**	**2a**	A	**19m**	33	22 (*S*)
14	4-$MeOC_6H_4$	**17n**	**2a**	A	**19n**	19	30 (*S*)
15	1-naphthyl	**17o**	**2a**	A	**19o**	34	41 (*S*)
16	$PhCH_2CH_2$	**17p**	**2a**	A	**19p**	17	50 (*S*)
17	3-$NO_2C_6H_4$	**17a**	**4**	B	**19a**	92	41 (*S*)
18	Ph	**17b**	**4**	B	**19b**	55	60 (*S*)
19	4-$NO_2C_6H_4$	**17d**	**4**	B	**19d**	87	42 (*S*)
20	4-ClC_6H_4	**17g**	**4**	B	**19g**	35	65 (*S*)
21	2-BrC_6H_4	**17g**	**4**	B	**19g**	68	77 (*S*)
22	2-MeC_6H_4	**17i**	**4**	B	**19i**	51	63 (*S*)
21	3-MeC_6H_4	**17j**	**4**	B	**19j**	25	61 (*S*)

[a] All reactions were performed on a 0.5 mmol scale with 5 mol % of ligand and 5 mol % of $Cu(OAc)_2·H_2O$ in 2 mL of *i*-PrOH (A) or *i*Pr/THF 1:1 (B) at room temperature for 98 h.
[b] Yields of isolated products.
[c] Enantiomeric excess was determined by HPLC using Chiracel OD-H column. The absolute configuration was assigned by comparing their specific rotations or the HPLC elution order with data from the literature.

The addition to *m*-nitrobenzaldehyde was carried out in moderate to good yield whereas the enantioselectivities were very low and did not exceed 29% for ligand **6b** (Table 3, entries 1–8). For comparison, phenanthro-1,2,4-triazine ligand **4** generated the β-nitro alcohol **19a** with an enantiomeric purity of 41%. The use of other 1,2,4-triazine-oxazoline ligands **1** investigated before afforded β-nitro alcohol **19a** with higher enantioselectivities of up to 49%.[5] In the presence of ligands **6a**–**b** possessing an indane moiety, benzaldehydes with a substituent at the *ortho*-position underwent the addition of nitromethane with relatively good enantioselection, but this was accompanied by low chemical yield (Table 3, entries 13–15). Previously examined 1,2,4-triazine-oxazoline ligand **1m** also with an indane unit catalysed the addition to *o*-bromo- and *o*-methylbenzaldehyde in yields of 81% and 66% and enantioselectivities of 77% and 92%, respectively.[5b] Although ligands **5e** and **5f** with an *N*-oxide moiety promoted the addition in good yield, the enantioselectivities obtained were very low (Table 3, entries 16 and 17). Thus, ligands with other than 1,2,4-triazine six-membered azaheteroaromatics were found to be less active in the asymmetric nitroaldol reaction than the 1,2,4-triazine-oxazoline ones. This suggests that the presence of a 1,2,4-triazine ring in the ligand structure is essential in promoting high levels of yield and enantioselection.

3. Conclusion

In conclusion, we have synthesised new 1,2,4-triazine-oxazoline ligands **2a**–**b** and **3** with a phenyl substituent at the 6-posision of the 1,2,4-triazine ring and ligand **4** with a phenanthro-fused 1,2,4-triazine. The ligands have been applied in the asymmetric addition of nitromethane to various aldehydes with enantioselectivities of up to 78%. The substitution mode of the 1,2,4-triazine ring was crucial in terms of the reactivity of the ligands mostly due to their solubility. Several ligands with different six-membered azaheteroaromatic rings instead of a 1,2,4-triazine ring have been synthesized. Two oxazoline ligands with an *N*-oxide function in the pyridine ring have also been obtained. Using these ligands in asymmetric nitroaldol reactions gave products with lower enantiomeric purities or yields, which indicates the important role of the 1,2,4-triazine ring in the enantioinduction. Studies to clarify the differences in the activity of the oxazoline ligands with a 1,2,4-triazine and with other azaheteroaromatics are currently in progress.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were determined at 400 and 100 MHz, respectively, with a Varian 400 MR spectrometer. Chemical shifts (δ) are reported in part per million from tetramethylsilane with the solvent resonance as the internal standard. Coupling constants are given as absolute values expressed in Hertz. Mass spectra were obtained by using AMD 604 (AMD Intectra GmbH, Germany) and GC/MS QP 5050 Shimadzu (30 m × 0.25 mm ID-BPX 5 0.25 mm) spectrometers. Infrared spectra were obtained by using a Shimadzu FT IR Affinity-1 Spectrometer. Elemental analyses were recorded with an Elementar Vario EL III CHNS analyser and the results for indicated elements were within 0.3% of the calculated values. Optical rotation values were measured at room temperature with a Perkin-Elmer polarimeter. The *ee* values were determined by HPLC (Knauer) analysis by using a chiral stationary phase column (Chiralcel OD-H or Chiralcel AD-H), and elution with isopropanol–hexanes. Thin layer chromatography (TLC) was carried out on aluminium sheets percolated with silica gel 60 F_{254} (Merck). Column chromatography separations were performed by using Merck Kieselgel 60 (0.040–0.060 mm). Solvents were dried and distilled according to standard procedures. 3-Chloro-6-phenyl-1,2,4-triazine[15] **14a** and 3-chlorophenanthro[9,10-*e*]-1,2,4-triazine[16] **14b** were synthesized according to literature procedures.

4.2. General procedure for the synthesis of 2-(*o*-aminophenyl) oxazolines 12a–b and 13

An oven dried two-necked flask was washed with argon and charged with 2-aminobenzonitrile (118 mg, 1 mmol), the appropriate amino alcohol, freshly flame dried $ZnCl_2$ (405 mg, 3 mmol) and anhydrous chlorobenzene (6 mL). The mixture was stirred at reflux for 24 h. The solvent was then removed under reduced pressure and the residue was stirred with 30% NaOH for 0.5 h. The product was extracted with dichloromethane and purified by flash column chromatography on silica gel.

4.2.1. 2-[(4*S*)-4-Phenyl-4,5-dihydro-1,3-oxazol-2-yl]aniline 12a

Compound **12a** was prepared from (*S*)-phenylglycinol (205 mg, 1.5 mmol) after purification by silica gel chromatography (hexane/EtOAc, 5:1), yield 90% (210 mg). All of the physical and spectroscopic data are with agreement with the published data.[17]

4.2.2. 2-[(4*S*)-4-Isopropyl-4,5-dihydro-1,3-oxazol-2-yl]aniline 12b

Compound **12b** was prepared from (*S*)-valinol (155 mg, 1.5 mmol) after purification by silica gel chromatography (hexane/EtOAc, 5:1), yield 74% (150 mg). All of the physical and spectroscopic data are with agreement with the published data.[17]

4.2.3. 2-[(3a*R*,8a*S*)-8,8a-Dihydro-3a*H*-indeno[1,2-*d*]oxazol-2-yl]-aniline 13

Compound **13** was prepared from (1*R*,2*S*)-1-amino-2-indanol (179 mg, 1.2 mmol) after purification by silica gel chromatography (hexane/EtOAc, 8:1), yield 58% (87 mg). All of the physical and spectroscopic data are in agreement with the published data.[18]

4.3. General procedure for the preparation of ligands 2a–b, 3, 4, 5a–d, 6a–c, 7, and 8

An oven dried three-necked flask was washed with argon and charged with Pd_2dba_3 (45.8 mg, 10 mol %), Xantphos (57.8 mg, 20 mol %), 2-(*o*-aminophenyl)oxazoline **12a**–**b** or **13** (0.6 mmol), heteroaromatic halide **14a**–**b** or **15a**–**c**, **16** (0.5 mmol) and K_2CO_3 (1.38 g, 10 mmol). The flask was then evacuated and backfilled with argon. Dioxane (10 mL) was added through the septum. The mixture was refluxed for the indicated period of time. After cooling, the solid material was filtered off and washed with CH_2Cl_2. The solvent was evaporated, and the resulting crude products were purified as described below.

4.3.1. 3-{2-[(4*S*)-4-Phenyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl} amino-6-phenyl-1,2,4-triazine 2a

The product was obtained from 3-chloro-6-phenyl-1,2,4-triazine **14a** and 2-[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl] aniline **12a** after 24 h of heating as a yellow solid. The product was purified by column chromatography using hexanes/ethyl acetate 10:1 and recrystallized from ethanol, yield 45% (88 mg). Mp 124–125 °C. $[\alpha]_D^{20}$ = +33.4 (*c* 0.55, CH_2Cl_2). IR (ZnSe) ν_{max}: 2999, 1627, 1543, 1442, 1425, 1041, 748, 690 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.73 (s, 1H), 9.01 (dd, *J* = 1.2, 8.8 Hz, 1H), 8.73 (s, 1H), 8.03–7.99 (m, 3H), 7.58–7.47 (m, 4H), 7.40–7.28 (m, 5H), 7.10 (dt, *J* = 1.2, 8.0 Hz, 1H), 5.62 (dd, *J* = 8.4, 10.4 Hz, 1H), 4.79 (dd, *J* = 8.4, 10.4 Hz, 1H), 4.25 (t, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.8, 159.3, 150.4, 147.1, 142.0, 140.6, 133.9, 132.7, 129.7, 129.6, 129.1, 128.8, 127.6, 126.5, 125.7, 121.1, 119.1, 112.7, 73.4, 69.9, 29.7. HRMS (ESI, *m*/*z*): calcd for $C_{24}H_{20}N_5O$ ($[M+H]^+$), 394.1662, found 394.1652.

4.3.2. 3-{2-[(4*S*)-4-Isopropyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl} amino-6-phenyl-1,2,4-triazine 2b

The product was obtained from 3-chloro-6-phenyl-1,2,4-triazine **14a** and 2-[(4*S*)-4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl]aniline **12b** after 24 h of heating as a yellow solid. The product was purified by column chromatography using hexanes/ethyl acetate 10:1 and recrystallized from ethanol, yield 32% (29 mg). Mp 138–139 °C. $[\alpha]_D^{20} = -7.1$ (*c* 0.50, CH_2Cl_2). IR (ZnSe) ν_{max}: 2958, 1633, 1543, 1423, 1039, 744 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 12.89 (s, 1H), 8.96 (dd, *J* = 0.8, 8.8 Hz, 1H), 8.76 (s, 1H), 8.04–8.02 (m, 2H), 7.91 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.55–7.48 (m, 4H), 7.06 (dt, *J* = 1.2, 8.0 Hz, 1H), 4.43 (dd, *J* = 8.4, 9.6 Hz, 1H), 4.28–4.24 (m, 1H), 4.11 (t, *J* = 8.0 Hz, 1H), 1.88 (o, *J* = 6.8 Hz, 1H), 1.13 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.3, 159.4, 150.3, 147.1, 143.3, 140.4, 134.0, 132.3, 130.5, 129.6, 129.4, 129.1, 128.9, 128.4, 125.7, 125.4, 120.9, 118.9, 113.0, 72.8, 69.3, 33.3, 19.0, 18.7. HRMS (ESI, *m*/*z*): calcd for $C_{21}H_{22}N_5O$ ($[M+H]^+$), 360.1819, found 360.1807. Anal. Calcd for $C_{21}H_{21}N_5O$ (359.17): C, 70.17; H, 5.89; N, 19.48. Found: C, 70.20; H, 5.98; N, 19.53.

4.3.3. 3-{2-[(3a*R*,8a*S*)-8,8a-Dihydro-3a*H*-indeno[1,2-*d*]oxazol-2-yl]phenyl}amino-6-phenyl-1,2,4-triazine 3

The product was obtained from 3-chloro-6-phenyl-1,2,4-triazine **14a** and 2-[(3a*R*,8a*S*)-8,8a-dihydro-3a*H*-indeno[1,2-*d*]oxazol-2-yl]-aniline **13** after 24 h of heating as a yellow solid. The product was purified by column chromatography using hexanes/ethyl acetate 4:1 and recrystallized from ethanol, yield 15% (28 mg). Mp 269–270 °C. $[\alpha]_D^{20} = -487.6$ (*c* 0.25, CH_2Cl_2). IR (ZnSe) ν_{max}: 3037, 1627, 1541, 1442, 1421, 1043, 746 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 12.71 (s, 1H), 8.89 (d, *J* = 7.6 Hz, 1H), 8.78 (s, 1H), 8.05–8.03 (m, 2H), 7.91 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.68–7.66 (m, 1H), 7.56 – 7.47 (m, 4H), 7.29–7.27 (m, 2H), 7.03 (t, *J* = 7.6 Hz, 1H), 5.93 (d, *J* = 7.6 Hz, 1H), 5.45 (dt, *J* = 1.6, 8.0 Hz, 1H), 3.54 (dd, *J* = 7.2, 18 Hz, 1H), 3.42 (d, *J* = 18.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.0, 159.4, 150.3, 147.0, 141.8, 140.3, 139.5, 134.0, 132.4, 129.6, 129.5, 129.1, 128.6, 127.6, 125.7, 125.3, 120.9, 118.9, 113.1, 81.9, 76.8, 39.5. HRMS (ESI, *m*/*z*): calcd for $C_{25}H_{20}N_5O$ ($[M+H]^+$), 406.1662, found 406.1662. Anal. Calcd for $C_{25}H_{19}N_5O{\cdot}1/2H_2O$ (414.16): C, 72.45; H, 4.86; N, 16.90. Found: C, 72.36; H, 4.82; N, 16.82.

4.3.4. 3-{2-[(4*S*)-4-Phenyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl} aminophenanthro[9,10-*e*]1,2,4-triazine 4

The product was obtained from 3-chlorophenanthro[9,10-*e*]-1,2,4-triazine **14b** and 2-[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]aniline **12a** after 20 h of heating as a yellow solid. The product was purified by washing with hot ethanol, yield 45% (105 mg). Mp 255–256 °C. $[\alpha]_D^{20} = +259.2$ (*c* 0.25, CH_2Cl_2). IR (ZnSe) ν_{max}: 3211, 3117, 2882, 1616, 1602, 1514, 1448, 1041, 748 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 13.14 (s, 1H), 9.33–9.30 (m, 1H), 9.22 (d, *J* = 8.4 Hz, 1H), 9.17 (dd, *J* = 1.2, 8.0 Hz, 1H), 8.59 (d, *J* = 8.4 Hz, 1H), 8.57–8.54 (m, 1H), 8.05 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.87 (dt, *J* = 1.2, 8.4 Hz, 1H), 7.77–7.69 (m, 4H), 7.45–7.38 (m, 4H), 7.33–7.30 (m, 1H), 7.15 (t, *J* = 7.2 Hz, 1H), 5.69 (t, *J* = 8.4 Hz, 1H), 4.84 (dd, *J* = 8.4, 10.4 Hz, 1H), 4.29 (t, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, TFA/benzene-d_6) δ: 172.3, 163.1, 154.6, 152.5, 139.2, 138.7, 138.6, 135.6, 133.7, 133.2, 132.9, 131.8, 131.0, 130.7, 130.1, 130.0, 129.8, 129.2, 128.7, 126.7, 125.4, 125.2, 124.7, 124.2, 79.7, 62.4. HRMS (ESI, *m*/*z*): calcd for $C_{30}H_{22}N_5O$ ($[M+H]^+$), 468.1819, found 468.1804.

4.3.5. 2-{2-[(4*S*)-4-Phenyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl} aminopyridine 5a

The product was obtained from 2-bromopyridine **15a** and 2-[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]aniline **12a** after 18 h of heating as a white solid. The product was purified by column chromatography using hexanes/ethyl acetate 9:1, yield 54% (85 mg). All of the physical and spectroscopic data of compound **5a** are in agreement with the published data.[13]

4.3.6. 2-{2-[(4*S*)-4-Phenyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl} aminopyrimidine 5b

The product was obtained from 2-chloropyrimidine **15b** and 2-[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]aniline **12a** after 19 h of heating as a white solid. The product was purified by column chromatography using hexanes/ethyl acetate 7:1, yield 55% (87 mg). Mp 83–84 °C. $[\alpha]_D^{20} = +376.5$ (*c* 1.0, CH_2Cl_2). IR (ZnSe) ν_{max}: 3230, 3062, 2971, 2900, 1635, 1608, 1558, 1531, 1436, 1406, 746, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 12.30 (s, 1H), 8.93 (d, *J* = 8.4 Hz, 1H), 8.45 (d, *J* = 4.8 Hz, 2H), 7.96 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.49 (dt, *J* = 1.2, 8.4 Hz, 1H), 7.36–7.28 (m, 5H), 7.02 (dt, *J* = 0.4, 7.6 Hz, 1H), 6.73 (t, *J* = 4.8 Hz, 1H), 5.60 (dd, *J* = 8.0, 10.0 Hz, 1H), 4.74 (dd, *J* = 8.8, 10.0 Hz, 1H), 4.20 (t, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.8, 160.2, 157.8, 142.3, 141.6, 132.4, 129.6, 128.7, 127.5, 126.5, 120.1, 118.5, 112.9, 112.3, 73.3, 70.0. HRMS (ESI, *m*/*z*): calcd for $C_{19}H_{17}N_4O$ ($[M+H]^+$), 317.1397, found 317.1394.

4.3.7. 2-{2-[(4*S*)-4-Phenyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl} aminopyrazine 5c

The product was obtained from 2-chloropyrazine **15c** and 2-[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]aniline **12a** after 3.5 h of heating as a white solid. The product was purified by column chromatography using hexanes/ethyl acetate 7:1, yield 92% (145 mg). Mp 71–72 °C. $[\alpha]_D^{20} = +351.5$ (*c* 1.0, CH_2Cl_2). IR (ZnSe) ν_{max}: 3176, 2966, 2900, 1626, 1521, 1448, 746 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 12.09 (s, 1H), 8.85 (dd, *J* = 0.8, 8.8 Hz, 1H), 8.17–8.14 (m, 2H), 7.97–7.96 (m, 1H), 7.94 (d, *J* = 1.6 Hz, 1H), 7.51 (ddd, *J* = 1.6, 7.2, 8.8 Hz, 1H), 7.41–7.30 (m, 5H), 7.01 (dt, *J* = 1.2, 8.4 Hz, 1H), 5.55 (dd, *J* = 8.4, 10.0 Hz, 1H), 4.77 (dd, *J* = 8.4, 10.0 Hz, 1H), 4.22 (t, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.2, 152.0, 142.1, 141.9, 141.1, 136.6, 134.9, 132.6, 129.7, 128.9, 127.8, 126.4, 120.0, 117.7, 111.9, 73.3, 69.9. HRMS (ESI, *m*/*z*): calcd for $C_{19}H_{17}N_4O$ ($[M+H]^+$), 317.1397, found 317.1395.

4.3.8. 2-{2-[(4*S*)-4-Isopropyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl} aminopyridine 5d

The product was obtained from 2-bromopyridine **15a** and 2-[(4*S*)-4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl]aniline **12b** after 21 h of heating as a white solid. The product was purified by column chromatography using hexanes/ethyl acetate 20:1, yield 21% (30 mg). All of the physical and spectroscopic data of compound **5d** are in agreement with the published data.[13]

4.3.9. 2-{2-[(3a*R*,8a*S*)-8,8a-Dihydro-3a*H*-indeno[1,2-*d*]oxazol-2-yl]phenyl}aminopyridine 6a

The product was obtained from 2-bromopyridine **15a** and 2-[(3a*R*,8a*S*)-8,8a-dihydro-3a*H*-indeno[1,2-*d*]oxazol-2-yl]-aniline **13** after 19 h of heating as a white solid. The product was purified by column chromatography using hexanes/ethyl acetate 10:1 and recrystallized from ethanol, yield 47% (78 mg). Mp 156–157 °C. $[\alpha]_D^{20} = -388.1$ (*c* 0.52, CH_2Cl_2). IR (ZnSe) ν_{max}: 3024, 1622, 1477, 1448, 1415, 746 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 11.52 (s, 1H), 8.70–8.67 (m, 1H), 8.28–8.26 (m, 1H), 7.82 (dd, *J* = 1.8, 8.0 Hz, 1H), 7.55–7.51 (m, 2H), 7.40–7.36 (m, 1H), 7.31–7.25 (m, 3H), 6.87–6.83 (m, 2H), 6.77 (ddd, *J* = 1.0, 5.0, 6.0 Hz, 1H), 5.84 (d, *J* = 7.8 Hz, 1H), 5.42 (ddd, *J* = 1.7, 6.7, 8.3 Hz, 1H), 3.52 (dd, *J* = 6.8, 18 Hz, 1H), 3.49 (dd, *J* = 1.2, 17.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.2, 155.3, 147.7, 142.7, 142.0, 139.7, 137.1, 132.2, 129.5, 128.5, 127.5, 125.4, 125.3, 118.8, 117.2, 115.4, 112.6, 111.5, 81.4, 76.8, 39.7. HRMS (ESI, *m*/*z*): calcd for $C_{21}H_{18}N_3O$ ($[M+H]^+$),

328.1444, found 328.1436. Anal. Calcd for $C_{21}H_{17}N_3O$ (327.13): C, 77.04; H, 5.23; N, 12.84. Found: C, 77.06; H, 5.25; N, 12.90.

4.3.10. 2-{2-[(3a*R*,8a*S*)-8,8a-Dihydro-3a*H*-indeno[1,2-*d*]oxazol-2-yl]phenyl}aminopyrimidine 6b

The product was obtained from 2-chloropyrimidine **15b** and 2-[(3a*R*,8a*S*)-8,8a-dihydro-3a*H*-indeno[1,2-*d*]oxazol-2-yl]-aniline **13** after 16 h of heating as a white solid. The product was purified by column chromatography using hexanes/ethyl acetate 8:1 and recrystallized from ethanol, yield 62% (102 mg). Mp 225–227 °C. $[\alpha]_D^{20} = -408.2$ (*c* 0.53, CH_2Cl_2). IR (ZnSe) ν_{max}: 3068, 1625, 1558, 1436, 1411, 744 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 12.08 (s, 1H), 8.83 (dd, *J* = 0.8, 8.4 Hz, 1H), 8.49 (d, *J* = 4.8 Hz, 2H), 7.86 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.66–7.64 (m, 1H), 7.43 (ddd, *J* = 1.6, 7.6, 8.8 Hz 1H), 7.30–7.25 (m, 3H), 6.94 (t, *J* = 8.0 Hz, 1H), 6.74 (t, *J* = 4.8 Hz, 1H), 5.91 (d, *J* = 8.0 Hz, 1H), 5.41 (ddd, *J* = 1.6, 6.4, 8.0 Hz, 1H), 3.52 (dd, *J* = 6.4, 18.0 Hz, 1H), 3.41 (d, *J* = 18.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.0, 160.3, 157.8, 142.0, 141.3, 139.6, 132.1, 129.5, 128.5, 127.5, 125.8, 125.2, 120.0, 118.4, 112.8, 112.6, 81.7, 76.8, 39.5. HRMS (ESI, *m*/*z*): calcd for $C_{20}H_{17}N_4O$ ($[M+H]^+$), 329.1397, found 329.1390. Anal. Calcd for $C_{20}H_{16}N_4O$ (328.13): C, 73.15; H, 4.91; N, 17.06. Found: C, 73.12; H, 5.01; N, 17.06.

4.3.11. 2-{2-[(3a*R*,8a*S*)-8,8a-Dihydro-3a*H*-indeno[1,2-*d*]oxazol-2-yl]phenyl}aminopyrazine 6c

The product was obtained from 2-chloropyrazine **15c** and 2-[(3a*R*,8a*S*)-8,8a-dihydro-3a*H*-indeno[1,2-*d*]oxazol-2-yl]-aniline **13** after 4 h of heating as a white solid. The product was purified by column chromatography using hexanes/ethyl acetate 8:1 and recrystallized from ethanol, yield 87% (143 mg). Mp 217–218 °C. $[\alpha]_D^{20} = -363.6$ (*c* 0.55, CH_2Cl_2). IR (ZnSe) ν_{max}: 3039, 1622, 1519, 1446, 1001, 746 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 12.04 (s, 1H), 8.76 (d, *J* = 8.4 Hz, 1H), 8.27 (s, 1H), 8.15 (s, 1H), 7.97 (d, *J* = 2.4 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 6.0 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.31–7.25 (m, 3H), 6.95 (t, *J* = 7.6 Hz, 1H), 5.86 (d, *J* = 8.0 Hz, 1H), 5.45 (t, *J* = 6.8 Hz, 1H), 3.54 (dd, *J* = 6.8, 18.0 Hz, 1H), 3.39 (d, *J* = 18.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.3, 152.1, 141.7, 141.6, 141.3, 139.6, 136.2, 134.3, 132.4, 129.6, 128.7, 127.7, 125.4, 125.2, 120.1, 117.8, 112.3, 81.8, 76.5, 39.7. HRMS (ESI, *m*/*z*): calcd for $C_{20}H_{17}N_4O$ ($[M+H]^+$), 329.1397, found 329.1388. Anal. Calcd for $C_{20}H_{16}N_4O$ (328.13): C, 73.15; H, 4.91; N, 17.06. Found: C, 79.96; H, 5.28; N, 17.06.

4.3.12. 2-Chloro-4-{2-[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl}aminopyrimidine 7

The product was obtained from 2,4-dichloropyrimidine **16** and 2-[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]aniline **12a** after 18 h of heating as a white solid. The product was purified by column chromatography using hexanes/ethyl acetate 7:1, yield 57% (100 mg). Mp 84–85 °C. $[\alpha]_D^{20} = +268.7$ (*c* 0.45, CH_2Cl_2). IR (ZnSe) ν_{max}: 3288, 3028, 2920, 1620, 1575, 1504, 1458, 1444, 1332, 1267, 981, 748, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 12.36 (s, 1H), 8.84 (d, *J* = 8.8 Hz, 1H), 8.09 (d, *J* = 5.6 Hz, 1H), 7.96 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.57 (ddd, *J* = 2.0, 7.6, 9.2 Hz, 1H), 7.42–7.29 (m, 5H), 7.11 (ddd, 0.8, 7.6, 8.4 Hz, 1H), 6.50 (d, *J* = 6.0 Hz, 1H), 5.53 (dd, *J* = 8.4, 10.0 Hz, 1H), 4.78 (dd, *J* = 8.4, 10.0 Hz, 1H), 4.22 (t, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.1, 161.1, 160.5, 156.8, 141.7, 140.3, 132.8, 129.6, 128.9, 127.9, 126.3, 121.8, 119.8, 113.0, 107.3, 73.5, 69.8. HRMS (ESI, *m*/*z*): calcd for $C_{19}H_{16}N_4OCl$ ($[M+H]^+$), 351.1007, found 351.1005.

4.3.13. 2,4-Di-{[2-((4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl)phenyl]amino}pyrimidine 8

The product was obtained from 2,4-dichloropyrimidine **16** and 2-[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]aniline **12a** after 30 h of heating as a white solid. The product was purified by column chromatography using hexanes/ethyl acetate 8:1, yield 16% (45 mg). Mp 64–65 °C. $[\alpha]_D^{20} = +349.7$ (*c* 0.45, CH_2Cl_2).^1H NMR (400 MHz, $CDCl_3$) δ: 12.05 (s, 1H), 11.87 (s, 1H), 8.94 (dd, *J* = 0.8, 8.4 Hz, 1H), 8.86–8.84 (m, 1H), 8.09 (d, *J* = 5.6 Hz, 1H), 7.94 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.90–7.87 (m, 1H), 7.49–7.29 (m, 11H), 7.00–6.89 (m, 3H), 6.14 (d, *J* = 5.6 Hz, 1H), 5.62 (t, *J* = 9.6 Hz, 1H), 5.53 (dd, *J* = 8.4, 9.6 Hz, 1H), 4.80–4.73 (m, 2H), 4.20–4.15 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.1, 164.9, 160.3, 159.6, 156.2, 142.4, 142.1, 142.0, 141.5, 132.3, 132.2, 129.5, 129.4, 128.9, 128.8, 127.7, 127.5, 126.5, 126.4, 120.4, 120.1, 119.6, 118.9, 112.4, 112.0, 101.5, 77.2, 73.3, 70.1, 69.9. HRMS (ESI, *m*/*z*): calcd for $C_{34}H_{29}N_6O_2$ ($[M+H]^+$), 553.2347, found 553.2344.

4.4. General procedure for the preparation of ligands 5e and 5f

2-{2-[(4*S*)-4-Phenyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl}aminopyridine **5a** or 2-{2-[(4*S*)-4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl}aminopyridine **5d** (0.5 mmol) was dissolved in dichloromethane (13 mL) and the solution was cooled to 0 °C. Next *m*-chloroperbenzoic acid (145 mg, 0.7 mmol) in dichloromethane (3 mL) was added dropwise and the mixture was stirred at 0 °C for 24 h. The mixture was then washed with sat. sodium bicarbonate three times. The organic layers were collected and dried over magnesium sulfate. After evaporation of the solvent, the crude products were purified by column chromatography (dichloromethane/methanol 80:1).

4.4.1. 2-{2-[(4*S*)-4-Phenyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl}aminopyridine 1-oxide 5e

The product was obtained from 2-{2-[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl}aminopyridine **5a** as a greenish oil, yield 51% (85 mg). $[\alpha]_D^{20} = +279.8$ (*c* 0.50, CH_2Cl_2). IR (ZnSe) ν_{max}: 3061, 1519, 1274, 1197, 742, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 11.92 (br s, 1H), 8.26 (dd, *J* = 5.6, 1.2 Hz, 1H), 8.00 (dd, *J* = 6.0, 1.6 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.50–7.46 (m, 2H), 7.44–7.41 (m, 3H), 7.37–7.33 (m, 2H), 7.18 (t, *J* = 8.0 Hz, 1H), 7.08 (dt, *J* = 1.2, 8.0 Hz, 1H), 6.74 (dt, *J* = 1.6, 6.4 Hz, 1H), 5.63 (t, *J* = 10.0 Hz, 1H), 4.79 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.25 (t, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.0, 148.1, 142.6, 140.5, 139.2, 132.5, 131.3, 129.3, 127.9, 127.7, 127.0, 122.1, 117.5, 116.0, 115.4, 110.2, 73.6, 70.2. HRMS (ESI, *m*/*z*): calcd for $C_{20}H_{18}N_3O_2$ ($[M+H]^+$), 553.2347, found 553.2344.

4.4.2. 2-{2-[(4*S*)-4-Isopropyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl}aminopyridine 1-oxide 5f

The product was obtained from 2-{2-[(4*S*)-4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl}aminopyridine **5d** as a greenish oil, yield 54% (80 mg). $[\alpha]_D^{20} = +43.2$ (*c* 0.54, CH_2Cl_2). IR (ZnSe) ν_{max}: 3061, 1519, 1275, 1197, 743, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 12.10 (br s, 1H), 8.28 (dd, *J* = 4.0, 1.4 Hz, 1H), 7.90 (dd, *J* = 6.4, 1.6 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.48 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.18 (t, *J* = 8.2 Hz, 1H), 7.03 (t, *J* = 7.2 Hz, 1H), 6.73 (t, *J* = 6.0 Hz, 1H), 4.40 (dd, *J* = 8.4, 0.8 Hz, 1H), 4.20 (t, *J* = 8.0 Hz, 1H), 4.10 (t, *J* = 8.0 Hz, 1H), 1.83 (o, *J* = 6.8 Hz, 1H), 1.16 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.9, 147.8, 139.7, 138.5, 131.5, 130.3, 127.1, 121.3, 116.6, 115.5, 114.7, 109.6, 73.2, 69.5, 33.4, 18.9, 18.8. HRMS (ESI, *m*/*z*): calcd for $C_{17}H_{20}N_3O_2$ ($[M+H]^+$), 298.1550, found 298.1549.

4.5. General procedure for the catalytic enantioselective Henry reaction

A mixture of $Cu(OAc)_2 \cdot H_2O$ (5 mg, 0.025 mmol, 5 mol %) and ligand (0.025 mmol, 5 mol %) in anhydrous 2-propanol (2 mL) or 2-propanol/THF, 1:1 was stirred at room temperature for 4 h under

argon atmosphere to give a red-brown solution. The aldehyde (0.5 mmol) and the nitromethane (270 μL, 5 mmol) were then added and the reaction was conducted at room temperature for 4 days. The solvent was then removed under reduced pressure and the product was isolated by column chromatography. All spectroscopic data of the nitroaldol adducts **19a**–**p** were in good agreement with those reported previously.[5] The ee values of the β-nitro alcohols **19a**–**p** were determined by chiral HPLC analysis. The absolute configurations of the products were assigned by comparing their specific rotations or the HPLC elution order with literature data.

4.5.1. (*S*)-2-Nitro-1-(3-nitrophenyl)ethanol 19a

Compound **19a** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 2.5:1) to give a colourless solid (97 mg, 92% yield). $[\alpha]_D^{20}$ = +17.1 (*c* 1.25, CH_2Cl_2). {Lit.[19a] $[\alpha]_D^{20}$ = +36.2 (*c* 1.25, CH_2Cl_2), 81% ee}. HPLC[20c] (Chiralcel OD-H, Hexane/*i*-PrOH = 90:10, flow rate: 1.0 mL/min, λ = 215 nm), t_{minor} = 21.1, t_{major} = 24.2, 41% ee.

4.5.2. (*S*)-2-Nitro-1-phenylethanol 19b

Compound **19b** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 7:1) to give a colourless oil (46 mg, 55% yield). $[\alpha]_D^{20}$ = +28.1 (*c* 1.00, CH_2Cl_2). {Lit.[20c] $[\alpha]_D^{20}$ = +40.2 (*c* 0.96, CH_2Cl_2), 98% ee}. HPLC[20c] (Chiralcel OD-H, Hexane/*i*-PrOH = 90:10, flow rate: 1.0 mL/min, λ = 215 nm), t_{minor} = 11.8, t_{major} = 14.5, 60% ee.

4.5.3. (*S*)-2-Nitro-1-(2-nitrophenyl)ethanol 19c

Compound **19c** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 5:1) to give a brown solid (90 mg, 85% yield). $[\alpha]_D^{20}$ = −98.5 (*c* 1.05, CH_2Cl_2). {Lit.[20c] $[\alpha]_D^{20}$ = −169.4 (*c* 0.22, CH_2Cl_2), 87% ee}. HPLC[20d] (Chiralcel OD-H, Hexane/*i*-PrOH = 90:10, flow rate: 1.0 mL/min, λ = 215 nm), t_{minor} = 11.7, t_{major} = 13.0, 43% ee.

4.5.4. (*S*)-2-Nitro-1-(4-nitrophenyl)ethanol 19d

Compound **19d** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 5:1) to give a colourless solid (90 mg, 87% yield). $[\alpha]_D^{20}$ = +18.2 (*c* 1.00, CH_2Cl_2). {Lit.[20c] $[\alpha]_D^{20}$ = +36.1 (*c* 0.98, CH_2Cl_2), 95% ee}. HPLC[20b] (Chiralcel OD-H, Hexane/*i*-PrOH = 85:15, flow rate: 1.0 mL/min, λ = 215 nm), t_{minor} = 13.5, t_{major} = 16.9, 42% ee.

4.5.5. (*S*)-1-(2-Chlorophenyl)-2-nitroethanol 19e

Compound **19e** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 7:1) to give a colourless oil (63 mg, 63% yield). $[\alpha]_D^{20}$ = +55.6 (*c* 1.03, CH_2Cl_2). {Lit.[20c] $[\alpha]_D^{20}$ = +47.7 (*c* 1.07, CH_2Cl_2), 99% ee}. HPLC[6b] (Chiralcel OD-H, Hexane/*i*-PrOH = 98:2, flow rate: 1.0 mL/min, λ = 215 nm), t_{minor} = 20.5, t_{major} = 22.0, 55% ee.

4.5.6. (*S*)-1-(3-Chlorophenyl)-2-nitroethanol 19f

Compound **19f** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 7:1) to give a colourless oil (41 mg, 41% yield). $[\alpha]_D^{20}$ = +17.4 (*c* 0.53, CH_2Cl_2). {Lit.[20c] $[\alpha]_D^{20}$ = +73.7 (*c* 0.48, CH_2Cl_2), 97% ee}. HPLC[20c] (Chiralcel OD-H, Hexane/*i*-PrOH = 90:10, flow rate: 1.0 mL/min, λ = 215 nm), t_{minor} = 12.5, t_{major} = 16.0, 29% ee.

4.5.7. (*R*)-1-(4-Chlorophenyl)-2-nitroethanol 19g

Compound **19g** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 7:1) to give a colourless oil (48 mg, 48% yield). $[\alpha]_D^{20}$ = −36.4 (*c* 1.02, CH_2Cl_2). {Lit.[19b] $[\alpha]_D^{20}$ = −48.1 (*c* 1.01, CH_2Cl_2), 95% ee}. HPLC[20a] (Chiralcel OD-H, Hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 215 nm), t_{minor} = 27.9, t_{major} = 22.1, 78% ee.

4.5.8. (*S*)-1-(2-Bromophenyl)-2-nitroethanol 19h

Compound **19h** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 8:1) to give a colourless oil (85 mg, 68% yield). $[\alpha]_D^{20}$ = +38.2 (*c* 0.90, CH_2Cl_2). {Lit.[20c] $[\alpha]_D^{20}$ = +46.2 (*c* 0.90, CH_2Cl_2), 98% ee}. HPLC[20d] (Chiralcel OD-H, Hexane/*i*-PrOH = 96:4, flow rate: 0.5 mL/min, λ = 215 nm), t_{minor} = 25.1, t_{major} = 26.6, 77% ee.

4.5.9. (*S*)-1-(2-Methylphenyl)-2-nitroethanol 19i

Compound **19i** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 10:1) to give a yellow oil (54 mg, 51% yield). $[\alpha]_D^{20}$ = +30.8 (*c* 1.01, CH_2Cl_2). {Lit.[20c] $[\alpha]_D^{20}$ = +52.8 (*c* 1.01, CH_2Cl_2), 99% ee}. HPLC[6b] (Chiralcel OD-H, Hexane/*i*-PrOH =90:10, flow rate: 1.0 mL/min, λ = 215 nm), t_{minor} = 10.3, t_{major} = 16.5, 63% ee.

4.5.10. (*S*)-1-(3-Methylphenyl)-2-nitroethanol 19j

Compound **19j** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 8:1) to give a yellow oil (23 mg, 25% yield). $[\alpha]_D^{20}$ = +23.2 (*c* 0.5, CH_2Cl_2). {Lit.[20c] $[\alpha]_D^{20}$ = +38.8 (*c* 0.50, CH_2Cl_2), 98% ee}. HPLC[6b] (Chiralcel OD-H, Hexane/*i*-PrOH = 90:10, flow rate: 1.0 mL/min, λ = 215 nm), t_{minor} = 10.1, t_{major} = 11.8, 61% ee.

4.5.11. (*S*)-1-(2-Methoxyphenyl)-2-nitroethanol 19l

Compound **19l** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 10:1) to give a yellow oil (16 mg, 16% yield). $[\alpha]_D^{20}$ = +29.2 (*c* 1.04, CH_2Cl_2). {Lit.[20c] $[\alpha]_D^{20}$ = +45.0 (*c* 1.05, CH_2Cl_2), 96% ee}. HPLC[6b] (Chiralcel OD-H, Hexane/*i*-PrOH =90:10, flow rate: 1.0 mL/min, λ = 215 nm), t_{minor} = 10.8, t_{major} = 13.1, 56% ee.

4.5.12. (*S*)-1-(3-Methoxyphenyl)-2-nitroethanol 19m

Compound **19m** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 7:1) to give a yellow oil (32 mg, 33% yield). $[\alpha]_D^{20}$ = +10.7 (*c* 0.60, CH_2Cl_2). {Lit.[20c] $[\alpha]_D^{20}$ = +36.3 (*c* 0.60, CH_2Cl_2), 92% ee}. HPLC[6b] (Chiralcel OD-H, Hexane/*i*-PrOH =90:10, flow rate: 1.0 mL/min, λ = 215 nm), t_{minor} = 22.2, t_{major} = 30.0, 22% ee.

4.5.13. (*S*)-1-(4-Methoxyphenyl)-2-nitroethanol 19n

Compound **19n** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 7:1) to give a yellow oil (19 mg, 19% yield). $[\alpha]_D^{20}$ = +15.3 (*c* 0.50, CH_2Cl_2). {Lit.[6b] $[\alpha]_D^{20}$ = +43.5 (*c* 0.95, CH_2Cl_2), 98% ee}. HPLC[6b] (Chiralcel OD-H, Hexane/*i*-PrOH =90:10, flow rate: 1.0 mL/min, λ = 215 nm), t_{minor} = 17.0, t_{major} = 21.5, 30% ee.

4.5.14. (*S*)-1-(1-Naphthyl)-2-nitroethanol 19o

Compound **19o** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 10:1) to give a yellow oil (36 mg, 34% yield). $[\alpha]_D^{20}$ = +26.8 (*c* 1.00, CH_2Cl_2). {Lit.[20c] $[\alpha]_D^{20}$ = +26.0 (*c* 1.06, CH_2Cl_2), 98% ee}. HPLC[20c] (Chiralcel OD-H, Hexane/*i*-PrOH = 90:10, flow rate: 1.0 mL/min, λ = 215 nm), t_{minor} = 15.0, t_{major} = 24.6, 41% ee.

4.5.15. (*S*)-1-Nitro-4-phenylbutan-2-ol 19p

Compound **19p** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 5:1) to give a colourless solid (16 mg, 17% yield). $[\alpha]_D^{20}$ = −4.8 (*c* 1.00, CH_2Cl_2). {Lit.[20c] $[\alpha]_D^{20}$ = −14.2 (*c* 1.00, CH_2Cl_2), 92% ee}. HPLC[6b] (Chiralpak AD-H, Hexane/*i*-PrOH = 95:5, flow rate: 0.7 mL/min, λ = 215 nm), t_{minor} = 27.9, t_{major} = 35.2, 50% ee.

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