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Asymmetric Henry reactions catalyzed by copper(II) complexes of chiral 1,2,4-triazine-oxazoline ligands: the impact of substitution in the oxazoline ring on ligand activity

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ABSTRACT

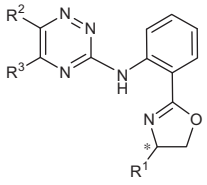
An enantiomerically pure 1,2,4-triazine-oxazoline ligand with an indanol-derived substituent in the oxazoline ring has been synthesized using Buchwald–Hartwig amination of 3-bromo-1,2,4-triazine. The catalytic efficiency of the ligand was estimated in the asymmetric nitroaldol (Henry) reaction of nitromethane with several aromatic and aliphatic aldehydes. The appropriate nitroaldol products were formed in good yields (up to 91%) and with up to 92% ee. In order to investigate the influence of the conformational rigidity and the additional stereocenter in the oxazoline ring on the catalytic activity of the ligand, a 1,2,4-triazine-oxazoline ligand with two phenyl substituents in the oxazoline ring was synthesized and tested in the asymmetric nitroaldol reaction.

1. Introduction

Chiral oxazoline ligands can form complexes with various metal ions; these complexes are excellent chiral catalysts in catalytic asymmetric reactions. Since the first report in 1986 on the use of chiral oxazoline based ligands, their applicability in asymmetric metal-catalyzed transformations has been demonstrated in numerous processes and has been reported in several comprehensive reviews devoted to this class of ligands.[1] A large number of papers concerning chiral oxazoline ligands have been published over the last year, thus proving the continued interest in these ligands. For example, spiro phosphine–oxazoline ligands were successfully applied in the asymmetric hydrogenation of cyclic α-alkylidene carbonyl compounds.[2] The high enantiocontrol of the oxazoline ligands arises from the fact that the stereogenic center of the ligands is situated next to the coordinating nitrogen atom of the oxazoline ring and therefore close to the metal active site having a direct influence on the stereochemical outcome of the process. Legault reported new iodoaryloxazoline catalysts bearing stereogenic center alpha to the oxazoline oxygen and proved their potential in catalyzing the enantioselective α-tosyloxylation of ketones.[3] Tartrate-derived bisoxazoline ligands have been recently found to be highly active in the asymmetric allylic alkylation reactions of various allyl acetates.[4] Bisoxazolines were also applied in the Ni-catalyzed asymmetric synthesis of a precursor to the drug Zoloft.[5]

During our research, we recently developed chiral 1,2,4-triazine-oxazoline ligands **1** (Fig. 1).[6] These ligands differ in the type of flexible substituent in the oxazoline ring and substitution in the 1,2,4-triazine.

The catalytic activity of the ligands was evaluated in the asymmetric nitroaldol reaction of nitromethane with a variety of aromatic and aliphatic aldehydes. The best enantioselectivity was achieved using ligand **1f**. The corresponding nitroaldol products were formed in yields of up to 95% and with enantioselectivities



1a - k

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

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

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0957-4166/

of 35–82%. The structure of ligand **1f** is composed of a 1,2,4-triazine with a phenyl ring at the 5-position and an oxazoline with a Ph substituent. In line with our interest in developing chiral ligands such as **1**, we decided to study the influence of the substitution in the oxazoline ring on the catalytic activity. Herein we report the synthesis and catalytic activity of ligand **2** incorporating the indane unit (Fig. 2). The indane ring prevents free rotation about the C—Ph bond, thus enforcing conformational rigidity.[7] Oxazolines with an indane unit were found to be highly effective chiral controllers for catalytic asymmetric Diels–Alder reactions[8] and Friedel–Crafts alkylation.[9] The structure of ligand **2** differs from ligand **1f** due to the additional stereocenter at the 5-position of the oxazoline ring. For comparison studies ligand **3** with two stereocenters in the oxazoline ring was synthesized (Fig. 2). In contrast to ligands **1a**–**c** and **1e**–**j**, ligands **2** and **3** possess an (*R*)-configured stereocenter at the 4-position of the oxazoline ring. The catalytic activity of ligands **2** and **3** in the asymmetric nitroaldol reaction is discussed.

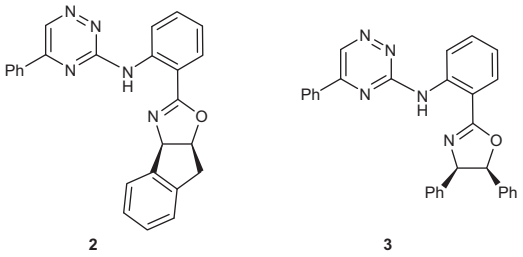


Figure 2. Ligands **2** and **3**.

2. Results and discussion

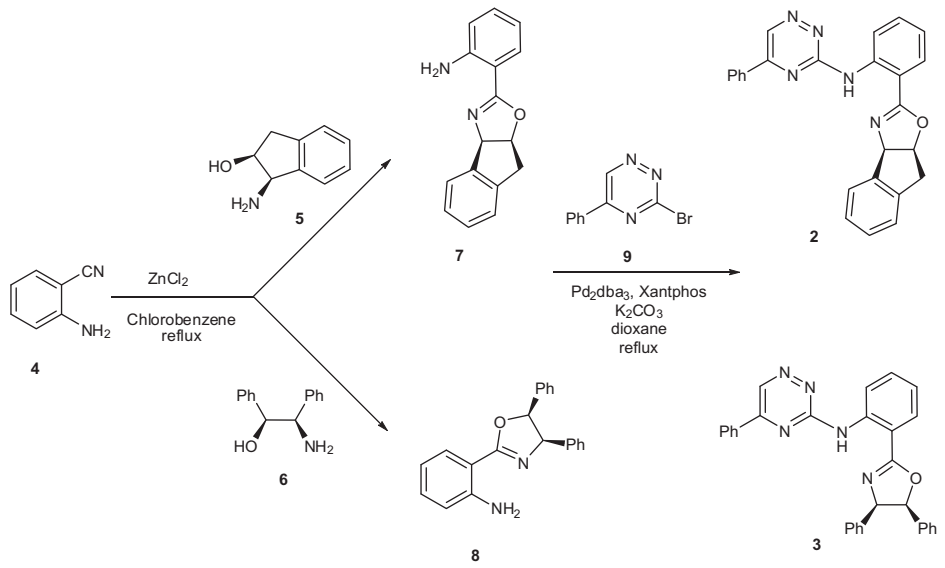
2.1. Synthesis of ligands

We envisaged that ligands **2** and **3** could be obtained by using the synthetic strategy adopted for the synthesis of ligands **1**. Accordingly, the synthesis began with the preparation of oxazoline derivatives **7** and **8** via the Zn-catalyzed condensation of 2-aminobenzonitrile with the appropriate enantiopure aminoalcohols (Scheme 1). A threefold excess of $ZnCl_2$ was used in the reactions, which shortened the reaction time to 24 h in comparison to experiments carried out with a catalytic amount of $ZnCl_2$.[10] Subsequent Buchwald–Hartwig amination of 3-bromo-5-phenyl-1,2,4-triazine **9** with oxazoline **7**[11] using Pd_2dba_3 as the palladium source and Xantphos as the ligand resulted in the formation of ligand **2** in 56% yield. An analogous reaction between triazine **9** and amino derivative **8** provided ligand **3** in 51% yield.

2.2. Enantioselective Henry reactions

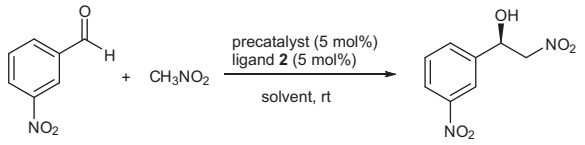
The asymmetric Henry reaction between 3-nitrobenzaldehyde and nitromethane was selected as a model reaction in order to evaluate the catalytic ability of ligand **2**. Initially, the reaction was investigated by using different metal salts and solvents at room temperature and the results are shown in Table 1.

It was observed that the type of precatalyst used had a significant effect on the yield and stereochemical outcome of the process. The application of $Cu(OAc)_2{\cdot}H_2O$ in 2-propanol provided the best results. The β-nitro alcohol was obtained in 71% yield and with 44% enantiomeric excess (Table 1, entry 1). Among the copper(I) precatalysts, only copper(I) thiopheno-2-carboxylate (CuTC) and copper(I) 3-methylsalicylate[12] (CuSal) catalyzed the nitroaldol reaction, but the yield of the product dropped dramatically to 61% and 36%, respectively. The reduction of the reaction yield was probably caused by the bulkiness of the carboxylate ions. The enantioselectivity of the reaction was unchanged when CuTC was used as the metal source (Table 1, entry 2). The application of CuSal afforded the product with a significantly higher enantioselectivity of 61% (Table 1, entry 3). Catalysts CuCl, $Cu(OTf)_2$, and $Zn(OTf)_2$ were inefficient in the asymmetric addition of nitromethane to 3-nitrobenzaldehyde (Table 1, entries 4–6). Next, the impact of solvent was studied. 2-Propanol promoted the highest enantioselectivity, although the yield was low due to the limited solubility in 2-propanol of the complexes generated (Table 1, entry 1). When THF was used as the reaction medium, the product was formed in a better yield of 82%, but with a much lower enantioselectivity of 12% in comparison to that obtained in 2-propanol (Table 1, entry 7). Similarly, the product was obtained in good yield but with a decrease in enantioselectivity when the mixture of 2-propanol and THF (1:2) was applied as the solvent (Table 1, entry 8). The enantioselectivity increased to 38% if the ratio of 2-propanol and THF was changed to 1:1 (Table 1, entry 9). Since the high-



Scheme 1. Synthesis of ligands **2** and **3**.

Table 1
Optimization of reaction conditions[a]

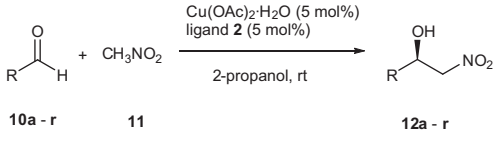


10a 11 12a

	Solvent	Precatalyst	Yield[b] %	ee[c] %
1	*i*-PrOH	$Cu(OAc)_2{\cdot}H_2O$	71	44 (*R*)
2	*i*-PrOH	CuTC[d]	61	44 (*R*)
3	*i*-PrOH	CuSal[e]	36	61 (*R*)
4	*i*-PrOH	CuCl	0	—
5	*i*-PrOH	$Cu(OTf)_2$	0	—
6	*i*-PrOH	$Zn(OTf)_2$	0	—
7	THF	$Cu(OAc)_2{\cdot}H_2O$	82	12 (*R*)
8	*i*-PrOH/THF (1:2)	$Cu(OAc)_2{\cdot}H_2O$	76	15 (*R*)
9	*i*-PrOH/THF (1:1)	$Cu(OAc)_2{\cdot}H_2O$	92	38 (*R*)

[a] All reactions were performed on a 0.5 mmol scale with 5 mol % of ligand and 5 mol % of precatalyst in 2 mL of solvent 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.
[d] Copper(I) thiopheno-2-carboxylate.
[e] Copper(I) 3-methylsalicylate.

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



10a - r 11 12a - r

	R	Aldehyde	Product	Yield[b] %	ee[c] %
1	$3\text{-}NO_2C_6H_4$	**10a**	**12a**	71	44 (*R*)
2	Ph	**10b**	**12b**	54	77 (*R*)
3	$2\text{-}NO_2C_6H_4$	**10c**	**12c**	73	62 (*R*)
4	$4\text{-}NO_2C_6H_4$	**10d**	**12d**	86	44 (*R*)
5	$2\text{-}ClC_6H_4$	**10e**	**12e**	75	77 (*R*)
6	$3\text{-}ClC_6H_4$	**10f**	**12f**	41	74 (*R*)
7	$4\text{-}ClC_6H_4$	**10g**	**12g**	47	78 (*R*)
8	$2\text{-}BrC_6H_4$	**10h**	**12h**	81	77 (*R*)
9[d]	$2\text{-}BrC_6H_4$	**10h**	**12h**	Traces	—
10	$2\text{-}MeC_6H_4$	**10i**	**12i**	66	92 (*R*)
11	$3\text{-}MeC_6H_4$	**10j**	**12j**	25	76 (*R*)
12	$4\text{-}MeC_6H_4$	**10k**	**12k**	57	77 (*R*)
13	$2\text{-}MeOC_6H_4$	**10l**	**12l**	91	76 (*R*)
14[d]	$2\text{-}MeOC_6H_4$	**10l**	**12l**	20	82 (*R*)
15	$3\text{-}MeOC_6H_4$	**10m**	**12m**	40	82 (*R*)
16	$4\text{-}MeOC_6H_4$	**10n**	**12n**	20	79 (*R*)
17	$3,4\text{-}(MeO)_2C_6H_4$	**10o**	**12o**	12	70 (*R*)
18	1-naphthyl	**10p**	**12p**	72	75 (*R*)
19	$PhCH_2CH_2$	**10q**	**12q**	42	60 (*R*)
20	$CH_3(CH_2)_3$	**10r**	**11r**	27	65 (*R*)

[a] All reactions were performed on a 0.5 mmol scale with 5 mol % of ligand and 5 mol % of $Cu(OAc)_2{\cdot}H_2O$ in 2 mL of 2-propanol at room temperature for 98 h.
[b] Yields of isolated products.
[c] Enantiomeric excess was determined by HPLC using Chiracel OD-H or AD-H column. The absolute configuration was assigned by comparing their specific rotations or the HPLC elution order with data from the literature.
[d] Reaction was carried out in the presence of copper(I) thiopheno-2-carboxylate (CuTC) instead of $Cu(OAc)_2{\cdot}H_2O$.

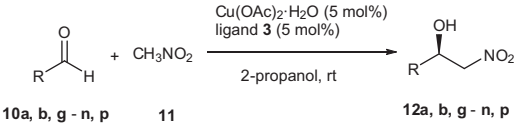
est enantioselectivity was generated in 2-propanol, it was chosen for further studies.

The scope of the nitroaldol reaction was examined under the optimized conditions described above. A variety of aldehydes were subjected to reaction with 10 equiv of nitromethane in the presence of 5 mol % of ligand **2** and $Cu(OAc)_2{\cdot}H_2O$ in 2-propanol at room temperature. The corresponding nitroaldol products were obtained in 12–91% yield. In all cases, the (*R*)-enantiomer was formed predominantly with enantiomeric excesses ranging from 44–92%.

Aldehydes substituted with electron-withdrawing groups underwent the addition of nitromethane in higher yield than benzaldehyde and aldehydes possessing electron-donating groups (Table 2, entries 1 and 3–8). The position of the substituent on the aromatic ring strongly affected the chemical yield of the reaction. When *ortho*-substituted aldehydes were subjected to the addition of nitromethane, the reaction rate was significantly higher, while substitution at the *meta*- or *para*-position resulted in a decreased yield. This generalization was not valid in the case of the three isomeric nitrobenzaldehydes, since 4-nitrobenzaldehyde was the most reactive among them (Table 2, entries 1, 3 and 4). The reactivity of methoxybenzaldehydes decreased in the order *ortho*, *meta*, and *para* (Table 2, entries 13, 15, and 16). Although, the lowest enentioselectivities were observed for nitrobenzaldehydes, the electronic nature of the substituents had little influence on the enantioselectivities. Inspection of Table 2 indicates, that for aldehydes possessing electron-withdrawing as well as electron-donating groups on the phenyl ring, high enantiomeric excesses were observed. However, 2-methylbenzaldehyde produced the Henry adduct with the highest enantioselectivity of 92% (Table 2, entry 10). Very good enantioselectivities of 72–89% were observed for methoxybenzaldehydes **10m**, **10n**, and **10l** (Table 2, entries 13–16). A relatively good yield (72%) and enantiomeric excess (75%) were obtained for 1-naphthaldehyde (Table 2, entry 18). The aliphatic aldehydes provided the respective nitroadduct in low yield and with moderate enantioselectivity (Table 1, entries 19 and 20). Benzaldehyde substituted with two methoxy groups gave the corresponding product in the lowest yield among the aldehydes screened (Table 2, entry 17). In addition, the impact of CuTC as a precatalyst in the addition of nitromethane to 2-bromo- and 2-methoxybenzaldehyde was examined. Only trace amounts of the product were formed in the reaction with 2-bromobenzaldehyde (Table 2, entry 9). The yield of reaction between nitromethane and 2-methoxybenzaldehyde catalyzed by **2**-CuTC dropped dramatically to 20% (Table 2, entry 14).

In comparison to our previously described ligand **1f**,[6] ligand **2** possesses better asymmetric induction abilities. The enantiomeric excesses observed using ligand **2** were significantly higher. Only three isomeric nitrobenzaldehydes gave the products with enantiomeric excesses similar to those obtained by using ligand **1f**. It is noteworthy that in the asymmetric addition of nitromethane to 4-chlorobenzaldehyde catalyzed by **1f**–$Cu(OAc)_2{\cdot}H_2O$ the expected nitroaldol product was not formed. The application of ligand **2** in the reaction resulted in the formation of product **12g** in 48% yield and with 78% ee (Table 2, entry 7). Similarly, only trace amounts of product **12n** were observed when 4-methoxybenzaldehyde was subjected to the addition of nitromethane in the presence of ligand **1f**. When the reaction was conducted in the presence of **2** product **12n** was isolated in better yield (Table 2, entry 16). Since ligand **2** has an opposite configuration of the stereocenter at the 4-position of the oxazoline ring, the (*R*)-enantiomers of the β-nitro alcohols were predominantly formed in comparison to those obtained by using **1f**. Slightly lower chemical yields were observed in reactions catalyzed by ligand **2** due to limited solubility of the complexes generated in 2-propanol. Improving the solubility by adding THF resulted in a decrease in the enantioselectivity (Table 1). The higher rate of enantioselectivity generated by ligand **2** could be due to two features: the conformational rigidity and/or presence of an additional stereocenter in the oxazoline ring of ligand **2**.

Table 3
Application of ligand **3** in the catalytic enantioselective Henry reaction[a]



10a, b, g - n, p **11** **12a, b, g - n, p**

	R	Aldehyde	Product	Yield[b] %	ee[c] %
1	3-$NO_2C_6H_4$	**10a**	**12a**	85	49 (*R*)
2	Ph	**10b**	**12b**	26	53 (*R*)
3	4-ClC_6H_4	**10g**	**12g**	61	59 (*R*)
4	2-BrC_6H_4	**10h**	**12h**	69	78 (*R*)
5	2-MeC_6H_4	**10i**	**12i**	65	53 (*R*)
6	3-MeC_6H_4	**10j**	**12j**	30	50 (*R*)
7	4-MeC_6H_4	**10k**	**12k**	40	49 (*R*)
8	2-$MeOC_6H_4$	**10l**	**12l**	81	68 (*R*)
9	3-$MeOC_6H_4$	**10m**	**12m**	52	54 (*R*)
10	4-$MeOC_6H_4$	**10n**	**12n**	17	43 (*R*)
11	1-Naphthyl	**10p**	**12p**	55	40 (*R*)

[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 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.

To investigate the role of the additional stereocenter, the catalytic activity of ligand **3** possessing two phenyl substituents in the oxazoline ring was evaluated. Ligand **3** was used in the Henry reaction between a few aromatic aldehydes and nitromethane. The results are reported in Table 3. Comparing these results with those summarized in Table 2, it is evident that ligand **3** possesses lower enantiocontrolling abilities than ligand **2**. In the presence of ligand **3**, the same level of enantioselectivity was observed only for 2-bromobenzaldehyde (Table 3, entry 4). The enantiomeric excesses of the products in reactions with other aldehydes were significantly lower than those obtained when using ligand **2**. The enantioselectivities obtained in reactions catalyzed by ligand **3** were similar to those generated by ligand **1f**.[6] This proves that a second stereocenter at the 5-position of the oxazoline ring of ligand **3** does not have any influence on the stereochemical outcome of the nitroaldol reaction. It can therefore be assumed that the impact of the additional stereocenter in ligand **2** on the enantioselectivity is insignificant, and that the enantioselectivities obtained in reactions catalyzed by this ligand are due to the conformational rigidity of its structure.

3. Conclusion

In conclusion, we have reported on the synthesis of a new 1,2,4-triazine-oxazoline ligand **2** with a restricted phenyl substituent at the 4-position of the oxazoline ring and ligand **3** with two phenyl substituents in the oxazoline. The synthesis was performed using Buchwald–Hartwig amination as the key step. The catalytic efficiency of both ligands was evaluated in the Cu-catalyzed asymmetric nitroaldol reaction. The enantiocontrol of ligand **2** predominates over the catalytic abilities of ligand **3**. It was proven that the presence of a second stereocenter in the oxazoline ring of ligands **2** and **3** had no effect on the enantioselectivity of the nitroaldol reaction. The enantioinduction generated by ligand **2** is governed by the conformational rigidity of its structure. Studies aimed at elucidating upon the transition state for the catalysis are currently in progress.

4. Experimental part

4.1. General

^1H 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 Magna FTIR—760 Nicolet apparatus and Shimadzu FT IR Affinity-1 Spectrometer. Elemental analyses were recorded with a Elementar Vario EL III CHNS analyzer 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 aluminum 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-Bromo-5-phenyl-1,2,4-triazine[13] **9** and copper(I) 3-methylsalicylate[12] were synthesized according to literature procedures.

4.2. Synthesis of 2-[(3a*R*,8a*S*)-8,8a-dihydro-3a*H*-indeno[1,2-*d*]-oxazol-2-yl]aniline 7 and 2-[(4*R*,5*S*)-4,5-diphenyl-4,5-dihydrooxazol-2-yl]aniline 8

An oven dried two-necked flask was washed with argon and charged with 2-aminobenzonitrile (118 mg, 1 mmol), (1*R*,2*S*)-1-amino-2-indanol **5** or (1*S*,2*R*)-2-amino-1,2-diphenylethanol **6** (1.2 mmol), 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 (hexane/EtOAc, 5:1).

4.2.1. 2-[(3a*R*,8a*S*)-8,8a-Dihydro-3a*H*-indeno[1,2-*d*]oxazol-2-yl]-aniline 7

All the physical and spectroscopic data of compound **7** are in agreement with the published ones.[14]

4.2.2. 2-[(4*R*,5*S*)-4,5-Diphenyl-4,5-dihydrooxazol-2-yl]aniline 8

The product was obtained from (1*S*,2*R*)-2-amino-1,2-diphenylethanol **6** as a white solid, yield 57% (178 mg). Mp 91–92 °C. $[\alpha]_D^{20} = -13.3$ (*c* 1.00, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.91 (dd, J = 1.2, 7.6 Hz, 1H), 7.29 (ddd, J = 1.6, 7.2, 8.4 Hz, 1H), 7.07–7.02 (m, 6H), 6.97–6.95 (m, 4H), 6.78 (dd, J = 0.4, 8.0 Hz, 1H), 6.74 (dt, J = 1.2, 8.4 Hz, 1H), 6.24 (br s, 2H), 5.92 (d, J = 10.0 Hz, 1H), 4.80 (d, J = 10.0 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 165.4, 148.9, 137.9, 136.5, 132.6, 130.0, 127.7, 127.65, 127.6, 127.4, 127.0, 126.4, 116.3, 115.9, 108.4, 83.6, 74.3. HRMS (ESI, *m*/*z*): calcd for $C_{21}H_{19}N_2O$ ([M+H]$^+$), 315.1492, found 315.1487.

4.3. General procedure for the synthesis of ligands 2 and 3

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 %), oxazoline derivative **7** or **8** (0.6 mmol), 3-bromo-5-phenyl-1,2,4-triazine **9** (118 mg, 0.5 mmol), and K_2CO_3 (1.38 g,

10 mmol). Next, the flask was evacuated and backfilled with argon. Dioxane (10 mL) was added via the septum after which the mixture was refluxed for 24 h. 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 by column chromatography using hexanes/ethyl acetate (10:1 for **2** and 5:1 for **3**) as the eluent and recrystallized from ethanol.

4.3.1. *N*-{2-[(3a*R*,8a*S*)-8,8a-Dihydro-3a*H*-indeno[1,2-*d*]oxazol-2-yl]pheny}-5-phenyl-1,2,4-triazin-3-amine 2

The product was obtained from 3-bromo-5-phenyl-1,2,4-triazine (**9**) and 2-[(3a*R*,8a*S*)-8,8a-dihydro-3a*H*-indeno[1,2-*d*]oxazol-2-yl]aniline **7** as a yellow solid, yield 56% (113 mg). Mp 240–241 °C. $[\alpha]_D^{20} = -408.4$ (*c* 0.55, CH_2Cl_2). IR (KBr) ν_{max}: 3422, 3006, 2930, 1629, 1507 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 12.65 (s, 1H), 9.23 (s, 1H), 8.92 (dd, *J* = 0.5, 8.4 Hz, 1H), 8.21–8.19 (m, 2H), 7.91 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.70–7.68 (m, 1H), 7.62–7.58 (m, 3H), 7.51 (ddd, *J* = 1.6, 7.2, 8.8 Hz, 1H), 7.29–7.27 (m, 3H), 7.03 (dt, *J* = 0.8, 8.0 Hz, 1H), 5.93 (d, *J* = 8.0 Hz, 1H), 5.47 (ddd, *J* = 1.6, 6.8, 8.0 Hz, 1H), 3.55 (dd, *J* = 6.4, 17.6 Hz, 1H), 3.42 (d, *J* = 18.0 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 163.9, 160.6, 155.4, 141.9, 140.6, 139.5, 139.0, 134.1, 132.3, 132.1, 129.5, 129.2, 128.6, 127.6, 127.5, 125.6, 125.3, 120.8, 119.0, 113.3, 81.9, 76.8, 39.6. HRMS (ESI, *m*/*z*): calcd for $C_{25}H_{20}N_5O$ ($[M+H]^+$), 406.1662, found 406.1657. Anal. calcd for $C_{25}H_{19}N_5O{\cdot}1/3H_2O$ (411.16): C, 72.98; H, 4.82; N, 17.02; found: C, 72.82; H, 5.00; N, 17.04.

4.3.2. *N*-{2-[(4*R*,5*S*)-4,5-Diphenyl-4,5-dihydrooxazol-2-yl]-phenyl}-5-phenyl-1,2,4-triazin-3-amine 3

The product was obtained from 3-bromo-5-phenyl-1,2,4-triazine **9** and 2-[(4*R*,5*S*)-4,5-diphenyl-4,5-dihydrooxazol-2-yl]aniline **8** as a yellow solid, yield 51% (120 mg). Mp 173–174 °C. $[\alpha]_D^{20} = -170.5$ (*c* 0.77, CH_2Cl_2). IR (ZnSe) ν_{max}: 3217, 3103, 3062, 3032, 2924, 2908, 1637, 1555, 1498, 1448 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 12.73 (s, 1H), 9.24 (s, 1H), 9.09 (dd, *J* = 0.8, 8.4 Hz, 1H), 8.15–8.12 (m, 3H), 7.68–7.62 (m, 1H), 7.57–7.50 (m, 3H), 7.16–7.12 (m, 1H), 7.09–7.03 (m, 8H), 6.99–6.97 (m, 2H), 6.02 (d, *J* = 10 Hz, 1H), 5.97 (d, *J* = 10 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 165.0, 160.5, 155.5, 141.0, 139.2, 137.4, 136.2, 133.8, 132.8, 132.1, 129.8, 129.2, 127.7, 127.7, 127.7, 127.6, 127.5, 126.9, 126.6, 121.1, 119.2, 112.8, 84.1, 74.3. HRMS (ESI, *m*/*z*): calcd for $C_{30}H_{24}N_5O$ ($[M+H]^+$), 470.1975, found 470.1962. Anal. calcd for $C_{30}H_{23}N_5O$ (469.19): C, 76.74; H, 4.94; N, 14.92; found: C,76.77; H, 5.03; N, 14.93.

4.4. 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 **2** or **3** (0.025 mmol, 5 mol %) in anhydrous 2-propanol (2 mL) was stirred at room temperature for 4 h under an argon atmosphere to give a red-brown solution. The aldehyde (0.5 mmol) and the nitromethane (270 μL, 5 mmol) were 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. The ee values of the nitroalcohols **12a**–**r** were determined by chiral HPLC analysis. The absolute configurations of the products were assigned by comparing their specific rotations or retention times in HPLC with literature data.

4.4.1. (*R*)-2-Nitro-1-(3-nitrophenyl)ethanol 12a

Compound **12a** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 2.5:1) to give a colorless solid (76 mg, 71% yield). $[\alpha]_D^{20} = -21.0$ (*c* 1.00, CH_2Cl_2). {Lit.[15] $[\alpha]_D^{20} = -32.8$ (*c* 1.00, CH_2Cl_2), 94% ee}. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.33 (s, 1H), 8.23 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 5.62–5.59 (m, 1H), 4.66–4.56 (m, 2H), 3.12 (d, *J* = 4.0 Hz, 1H). HPLC[16] (Chiralcel OD-H, Hexane/*i*-PrOH = 90:10, flow rate: 1.0 mL/min, λ = 215 nm), t_{major} = 28.4, t_{minor} = 33.0, 44% ee.

4.4.2. (*R*)-2-Nitro-1-phenylethanol 12b

Compound **12b** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 7:1) to give a colorless oil (45 mg, 54% yield). $[\alpha]_D^{20} = -42.5$ (*c* 1.00, CH_2Cl_2). {Lit.[17] $[\alpha]_D^{20} = -53.1$ (*c* 1.01, CH_2Cl_2), 96% ee}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.42–7.36 (m, 5H), 5.47 (d, *J* = 8.8 Hz, 1H), 4.65–4.51 (m, 2H), 2.79 (br s, 1H). HPLC[18] (Chiralcel OD-H, Hexane/*i*-PrOH = 90:10, flow rate: 1.0 mL/min, λ = 215 nm), t_{major} = 14.4, t_{minor} = 17.8, 77% ee.

4.4.3. (*R*)-2-Nitro-1-(2-nitrophenyl)ethanol 12c

Compound **12c** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 5:1) to give a brown solid (77 mg, 73% yield). $[\alpha]_D^{20} = +147.5$ (*c* 0.23, CH_2Cl_2). {Lit.[19] $[\alpha]_D^{20} = +225.3$ (*c* 0.25, CH_2Cl_2), 96% ee}. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.08 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.95 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.77–7.73 (m, 1H), 7.58–7.53 (m, 1H), 6.07–6.03 (m, 1H), 4.89 (dd, *J* = 2.4, 14.0 Hz, 1H), 4.57 (dd, *J* = 9.2, 14.0 Hz, 1H), 3.18 (d, *J* = 4.4 Hz, 1H). HPLC[20] (Chiralcel OD-H, Hexane/*i*-PrOH = 90:10, flow rate: 1.0 mL/min, λ = 215 nm), t_{major} = 16.1, t_{minor} = 18.7, 62% ee.

4.4.4. (*R*)-2-Nitro-1-(4-nitrophenyl)ethanol 12d

Compound **12d** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 5:1) to give a colorless solid (91 mg, 86% yield). $[\alpha]_D^{20} = -21.1$ (*c* 0.30, CH_2Cl_2). {Lit.[19] $[\alpha]_D^{20} = -35.1$ (*c* 0.24, CH_2Cl_2), 92% ee}. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.27 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.6 Hz, 2H), 5.62–5.59 (m, 1H), 4.64–4.58 (m, 2H), 3.12 (d, *J* = 4.0 Hz, 1H). HPLC[20] (Chiralcel OD-H, Hexane/*i*-PrOH = 85:15, flow rate: 1.0 mL/min, λ = 215 nm), t_{major} = 17.6, t_{minor} = 22.5, 44% ee.

4.4.5. (*R*)-1-(2-Chlorophenyl)-2-nitroethanol 12e

Compound **12e** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 7:1) to give a colorless oil (75 mg, 75% yield). $[\alpha]_D^{20} = -46.6$ (*c* 2.50, CH_2Cl_2). {Lit.[21] $[\alpha]_D^{20} = -47.3$ (*c* 2.85, CH_2Cl_2), 83% ee}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.67 (dd, *J* = 2.0, 7.6 Hz, 1H), 7.40–7.28 (m, 3H), 5.88–5.84 (m, 1H), 4.68 (dd, *J* = 2.4, 14.0 Hz, 1H), 4.46 (dd, *J* = 9.6, 14.0 Hz, 1H), 2.96 (dd, *J* = 0.4, 4.4 Hz, 1H). HPLC[22] (Chiralcel OD-H, Hexane/*i*-PrOH = 98:2, flow rate: 1.0 mL/min, λ = 208 nm), t_{major} = 27.8, t_{major} = 30.6, 77% ee.

4.4.6. (*R*)-1-(3-Chlorophenyl)-2-nitroethanol 12f

Compound **12f** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 7:1) to give a colorless oil (41 mg, 41% yield). $[\alpha]_D^{20} = -31.2$ (*c* 0.50, $CHCl_3$). {Lit.[23] $[\alpha]_D^{20} = -36.6$ (*c* 0.55, $CHCl_3$), 92% ee}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.44–7.43 (m, 1H), 7.35–7.34 (m, 2H), 7.30–7.27 (m, 1H), 5.48–5.44 (m, 1H), 4.59 (dd, *J* = 9.2, 13.6 Hz, 1H), 4.52 (dd, *J* = 3.2, 13.6 Hz, 1H), 2.87 (d, *J* = 4.0 Hz, 1H). HPLC[16] (Chiralcel OD-H, Hexane/*i*-PrOH = 90:10, flow rate: 1.0 mL/min, λ = 215 nm), t_{minor} = 12.2, t_{major} = 15.8, 74 % ee.

4.4.7. (*R*)-1-(4-Chlorophenyl)-2-nitroethanol 12g

Compound **12g** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 7:1) to give a colorless oil 47 mg, 47% yield). $[\alpha]_D^{20} = -36.9$ (*c* 1.76, CH_2Cl_2). {Lit.[17] $[\alpha]_D^{20} = -48.1$ (*c* 1.01, CH_2Cl_2), 95% ee}. ^1H

NMR (400 MHz, $CDCl_3$) δ: 7.40–7.34 (m, 4H), 5.48–5.43 (m, 1H), 4.59 (dd, J = 9.6, 13.6 Hz, 1H), 4.49 (dd, J = 3.2, 13.6 Hz, 1H), 2.87 (d, J = 3.6, Hz, 1H). HPLC[16] (Chiralcel OD-H, Hexane/*i*-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 215 nm), t_{major} = 28.5.1, t_{major} = 37.0, 78% ee.

4.4.8. (*R*)-1-(2-Bromophenyl)-2-nitroethanol 12h

Compound **12h** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 8:1) to give a colorless oil (100 mg, 81% yield). $[\alpha]_D^{20}$ = −38.6 (*c* 1.00, CH_2Cl_2). {Lit.[20] $[\alpha]_D^{20}$ = −35.2 (*c* 1.0, CH_2Cl_2), 89% ee}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (dd, J = 1.6, 7.6 Hz, 1H), 7.57 (dd, J = 1.2, 8.0 Hz, 1H), 7.41 (dt, J = 1.6, 7.6 Hz, 1H), 7.23 (dt, J = 1.6, 7.6 Hz, 2H), 5.81 (dd, J = 1.6, 9.6 Hz, 1H), 4.69 (dd, J = 2.0, 13.6 Hz, 1H), 4.44 (dd, J = 9.6, 13.6 Hz, 1H), 3.00 (brs, 1H). HPLC[16] (Chiralcel OD-H, Hexane/*i*-PrOH = 95:5, flow rate: 0.5 mL/min, λ = 215 nm), t_{major} = 30.9, t_{minor} = 34.4, 77% ee.

4.4.9. (*R*)-1-(2-Methylphenyl)-2-nitroethanol 12i

Compound **12i** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 10:1) to give a yellow oil (60 mg, 66% yield). $[\alpha]_D^{20}$ = −45.1 (*c* 1.00, CH_2Cl_2). {Lit.[24] $[\alpha]_D^{20}$ = −45.8 (*c* 1.0, CH_2Cl_2), 91% ee}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.54–7.52 (m, 1H), 7.29–7.24 (m, 2H), 7.21–7.18 (m, 1H), 5.71–5.68 (m, 1H), 4.57 (dd, J = 9.6, 13.2 Hz, 1H), 4.45 (dd, J = 2.8, 13.6 Hz, 1H), 2.64 (d, J = 3.6 Hz, 1H), 2.40 (s, 3H). HPLC[16] (Chiralcel OD-H, Hexane/*i*-PrOH = 90:10, flow rate: 1.0 mL/min, λ = 215 nm), t_{major} = 11.4, t_{minor} = 18.0, 92% ee.

4.4.10. (*R*)-1-(3-Methylphenyl)-2-nitroethanol 12j

Compound **12j** 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). $[\alpha]_D^{20}$ = −21.2 (*c* 0.30, CH_2Cl_2). {Lit.[25] $[\alpha]_D^{20}$ = −32.2 (*c* 0.3, CH_2Cl_2), 93% ee}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (t, J = 7.6 Hz, 1H), 7.22–7.17 (m, 3H), 5.44–5.42(m, 1H), 4.61 (dd, J = 9.6, 13.6 Hz, 1H), 4.51 (dd, J = 2.8, 13.6 Hz, 1H), 2.75 (d, J = 3.2, 1H), 2.38 (s, 3H). HPLC[16] (Chiralcel OD-H, Hexane/*i*-PrOH = 90:10, flow rate: 1.0 mL/min, λ = 215 nm), t_{major} = 12.3, t_{minor} = 14.4, 76% ee.

4.4.11. (*R*)-1-(4-Methylphenyl)-2-nitroethanol 12k

Compound **12k** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 5:1) to give a yellow oil (52 mg, 57% yield). $[\alpha]_D^{20}$ = −34.4 (*c* 1.00, CH_2Cl_2). {Lit.[18] $[\alpha]_D^{20}$ = −44.3 (*c* 1.0, CH_2Cl_2), 91% ee}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 5.45– 5.41 (m, 1H), 4.62 (dd, J = 9.6, 13.2 Hz, 1H), 4.49 (dd, J = 3.2, 13.2 Hz, 1H), 2.76 (br s, 1H), 2.36 (s, 3H). HPLC[16] (Chiralcel OD-H, Hexane/*i*-PrOH = 90:10, flow rate: 1.0 mL/min, λ = 215 nm), t_{major} = 14.5, t_{minor} = 18.9, 77% ee.

4.4.12. (*R*)-1-(2-Methoxyphenyl)-2-nitroethanol 12l

Compound **12l** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 10:1) to give a yellow oil (91 mg, 91% yield). $[\alpha]_D^{20}$ = −38.4 (*c* 1.00, CH_2Cl_2). {Lit.[17] $[\alpha]_D^{20}$ = −48.9 (*c* 0.99, CH_2Cl_2), 96% ee}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44 (dd, J = 1.2, 7.6 Hz, 1H), 7.33 (dt, J = 1.6, 8.0 Hz, 1H), 7.02 (dt, J = 0.8, 7.6 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 5.65–5.62 (m, 1H), 4.65 (dd, J = 3.2, 13.2 Hz, 1H), 4.58 (dd, J = 9.2, 13.2 Hz, 1H), 3.89 (s, 3H), 3.11 (d, J = 6.0 Hz, 1H). HPLC[16] (Chiralcel OD-H, Hexane/*i*-PrOH = 90:10, flow rate: 1.0 mL/min, λ = 215 nm), t_{major} = 11.6, t_{minor} = 13.8, 76% ee.

4.4.13. (*R*)-1-(3-Methoxyphenyl)-2-nitroethanol 12m

Compound **12m** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 7:1) to give a yellow oil (40 mg, 40% yield). $[\alpha]_D^{20}$ = −30.3 (*c* 0.30, CH_2Cl_2). {Lit.[17] $[\alpha]_D^{20}$ = −38.8 (*c* 0.99, CH_2Cl_2), 94% ee}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34–7.30 (m, 1H), 6.97–6.96 (m, 2H), 6.91–6.88 (m, 1H), 5.47–5.43 (m, 1H), 4.60 (dd, J = 9.6, 13.6 Hz, 1H), 4.51 (dd, J = 3.2, 13.6 Hz, 1H), 3.83 (s, 3H), 2.76 (br s, 1H). HPLC[16] (Chiralcel OD-H, Hexane/*i*-PrOH = 90:10, flow rate: 1.0 mL/min, λ = 215 nm), t_{major} = 23.7, t_{minor} = 30.8, 82% ee.

4.4.14. (*R*)-1-(4-Methoxyphenyl)-2-nitroethanol 12n

Compound **12n** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 7:1) to give a yellow oil (20 mg, 20% yield). $[\alpha]_D^{20}$ = −38.0 (*c* 0.50, CH_2Cl_2). {Lit.[17] $[\alpha]_D^{20}$ = −47.1 (*c* 1.0, CH_2Cl_2), 92% ee}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32 (d, J = 8.8 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 5.48–5.41 (m, 1H), 5.40–5.43 (m, 1H), 4.59 (dd, J = 9.6, 13.2 Hz, 1H), 4.49 (dd, J = 2.4, 13.0 Hz, 1H), 3.82 (br s, 3H), 2.78 (d, J = 3.2 Hz, 1H). HPLC[16] (Chiralcel OD-H, Hexane/*i*-PrOH = 90:10, flow rate: 1.0 mL/min, λ = 215 nm), t_{major} = 21.5, t_{minor} = 28.1, 79% ee.

4.4.15. (*R*)-1-(3,4-Dimethoxyphenyl)-2-nitroethanol 12o

Compound **12o** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 2.5:1) to give a yellow oil (14 mg, 12% yield). $[\alpha]_D^{20}$ = −22.3 (*c* 0.44, CH_2Cl_2). {Lit.[20] $[\alpha]_D^{20}$ = −24.6 (*c* 1.0, CH_2Cl_2), 89% ee}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.93–6.84 (m, 3H), 5.41 (dd, J = 4.0, 12.0 Hz, 1H), 4.60 (dd, J = 12.0, 16.0 Hz, 1H), 4.50 (dd, J = 4.0, 12.0 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 2.73 (br s, 1H). HPLC[18] (Chiralcel OD-H, Hexane/*i*-PrOH = 85:15, flow rate: 1.0 mL/min, λ = 215 nm), t_{major} = 29.8, t_{minor} = 40.7, 70% ee.

4.4.16. (*R*)-1-(1-Naphthyl)-2-nitroethanol 12p

Compound **12p** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 10:1) to give a yellow oil (78 mg, 72% yield). $[\alpha]_D^{20}$ = −22.8 (*c* 1.00, CH_2Cl_2). {Lit.[17] $[\alpha]_D^{20}$ = −30.6 (*c* 1.1, CH_2Cl_2), 93% ee}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.62–7.51 (m, 3H), 6.61–6.58 (m, 1H), 4.75–4.64 (m, 2H), 2.82 (d, J = 3.6 Hz, 1H). HPLC[20] (Chiralcel OD-H, Hexane/*i*-PrOH = 90:10, flow rate: 1.0 mL/min, λ = 215 nm), t_{major} = 18.8, t_{major} = 27.9, 75% ee.

4.4.17. (*R*)-1-Nitro-4-phenylbutan-2-ol 12q

Compound **12q** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 5:1) to give a colorless solid (41 mg, 42% yield). $[\alpha]_D^{20}$ = +9.2 (*c* 1.00, CH_2Cl_2). {Lit.[24] $[\alpha]_D^{20}$ = +12.03 (*c* 1.00, CH_2Cl_2), 92% ee}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33–7.29 (m, 2H), 7.24–7.19 (m, 3H), 4.41–4.39 (m, 2H), 4.36–4.28 (m, 1H), 2.90–2.83 (m, 1H), 2.79–2.71 (m, 1H), 2.57 (d, J = 4.8 Hz, 1H), 1.92–1.75 (m, 2H). HPLC[24] (Chiralpak AD-H, Hexane/*i*-PrOH = 90:10, flow rate: 1.0 mL/min, λ = 215 nm), t_{major} = 11.2, t_{minor} = 14.2, 60% ee.

4.4.18. (*B*)-1-Nitrohexan-2-ol 12r

Compound **12r** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 5:1) to give a yellow oil (20 mg, 27% yield). $[\alpha]_D^{20}$ = −7.0 (*c* 0.40, CH_2Cl_2). {Lit.[26] $[\alpha]_D^{20}$ = −9.2 (*c* 0.6, CH_2Cl_2), 94% ee}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.42 (dd, J = 2.4, 12.8 Hz, 1H), 4.40–4.35 (m, 1H), 4.34–4.29 (m, 1H), 2.59 (br s, 1H), 1.59–1.42 (m, 3H), 1.41–1.32 (m, 3H), 0.92 (t, J = 7.2 Hz, 3H). HPLC[27] (Chiralpak AD-H, Hexane/*i*-PrOH = 98:2, flow rate: 0.8 mL/min, λ = 215 nm), t_{major} = 31.3, t_{minor} = 41.8, 65% ee.

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