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Chiral oxazoline ligands containing a 1,2,4-triazine ring and their application in the Cu-catalyzed asymmetric Henry reaction

Ewa Wolińska *

Department of Chemistry, Siedlce University, 08-110 Siedlce, Poland

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ABSTRACT

Eleven members of new ligand class incorporating a chiral oxazoline and a 1,2,4-triazine ring have been synthesized via Pd-catalyzed amination reaction of 3-halo-1,2,4-triazines with 2-(*o*-aminophenyl)oxazolines. Buchwald–Hartwig amination of 3-halo-1,2,4-triazines was investigated to establish the best conditions for synthesis of the title ligands. Catalytic activity of the new ligands was evaluated in the asymmetric Henry reaction of nitromethane with a variety of aromatic and aliphatic aldehydes. The β-hydroxy nitroalkanes were obtained in high yields (up to 95%), and moderate-to-good enantioselectivity (up to 82% ee).

1. Introduction

The nitroaldol (Henry)[1] reaction has become a powerful synthetic method for carbon–carbon bond formation in which a nitroalkane compound is added to an aldehyde or ketone to give a β-nitro alcohol. The resulting β-nitro alcohols can be further converted into valuable bifunctional compounds, such as β-amino alcohols by reduction of the nitro group, and α-hydroxycarboxylic acids by the Nef reaction.[2] Furthermore, the enantioselective addition of nitroalkanes to carbonyl compounds provides optically active β-nitroalkanols, which are useful intermediates in the asymmetric synthesis of pharmacologically important compounds.[3] Since the first asymmetric version of the Henry reaction was reported by Shibasaki,[4] metal-catalyzed enantioselective nitroaldol reaction has attracted much attention and various efficient chiral ligands have been elaborated for this synthetically useful method.[5]

Chiral oxazolines are a type of 'privileged ligands' and their applicability was proven with great success in various asymmetric metal-catalyzed transformations including enantioselective diethylzinc additions to aldehydes, Diels–Alder reactions, cyclopropanations, hydrosilylations, hydrogenations and allylic alkylations.[6] Modular oxazoline ligands have also been applied with great success in the asymmetric Henry reaction.[7] A large number of pyridyl chiral oxazolines and bisoxazolines have been used as ligands for metal-catalyzed enantioselective transformations.[6] Oxazoline ligands containing thiophene,[8] quinoline,[9] quinazoline,[10] pyrrolidine[11] and phthalazine[12] rings have also been described. Very recently, new pyrrole-oxazoline ligands have been synthesized and tested in an asymmetric nitroaldol reaction.[7a]

Therefore, the chiral oxazolines with an appropriate functionality offer an excellent framework for the design of novel ligands, which can form catalysts with metals containing more than one active centre. Such catalysts exhibit both Lewis acidity and Lewis basicity and have been developed as highly active and stereoselective bifunctional catalysts. The concept of bifunctional activation has recently become a fast growing area of asymmetric catalysis.[13] Surprisingly, there are only a few examples of oxazoline-containing complexes with different metals showing synergistic activation of electrophilic and nucleophilic centres.[14] New types of oxazoline-pyridine-based bifunctional complexes have been described by Guiry.[14a]

To the best of our knowledge, chiral oxazolines containing a 1,2,4-triazine ring have not been synthesized and used as ligands in asymmetric synthesis. It is well known that 1,2,4-triazines are powerful metal chelators[15] and have been used, inter alia, as selective extractants of rare elements from nuclear waste.[16] So, we envisaged that 1,2,4-triazine nitrogen atoms can coordinate together with an oxazoline nitrogen atom to form stable complexes. Moreover, 1,2,4-triazine nitrogen atoms can act as Lewis bases, thus the oxazoline-1,2,4-triazine ligands can form bifunctional catalysts with metals.

* Tel.: +48 25 6431116; fax: +48 25 6442095; e-mail addresses: ewol@uph.edu.pl. ewawoli@yahoo.com.

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Here, we report on the synthesis of ligand class **9** in which an *N*-phenylamine unit links the 1,2,4-triazine and chiral oxazoline rings. The application of these ligands as chiral auxiliaries in the asymmetric Henry reaction is also described.

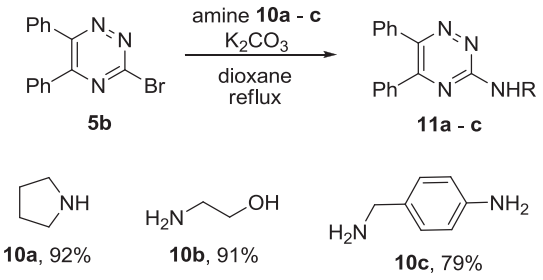
2. Results and discussion

2.1. Synthesis of chiral ligands

Two possible synthetic approaches leading to ligands **9** are outlined in Scheme 1. Our initial strategy was based on the palladium-catalysed cross-coupling reaction of 2-chlorobenzonitrile (**2**) and 3-amino-1,2,4-triazine (**1a**, R^2=R^3=H) followed by generation of the chiral oxazoline ring by condensation of an enantiomerically pure amino alcohol and the nitrile group of compound **3** (Scheme 1, route A). It was reported by Guillaument et al.[17] that electron poor 3-amino-1,2,4-triazine (**1a** R^2=R^3=H) easily coupled with a variety of heteroaryl chlorides employing Buchwald–Hartwig amination[18] using mixtures of Xantphos and $Pd(OAc)_2$ or Pd_2dba_3 as the palladium source. Unfortunately, attempts to extend this protocol to the Pd-catalysed amination starting from 2-chlorobenzonitrile (**2**) and 3-amino-1,2,4-triazine (**1a**, R^2=R^3=H) were unsuccessful and only 3-amino-1,2,4-triazine was recovered unchanged. It seems likely that the chloro substituent in 2-chlorobenzonitrile does not act as a good leaving group under Buchwald–Hartwing amination conditions with poor nucleophile **1a**. Therefore, we directed our attention to the Pd-catalysed cross-coupling reaction of the corresponding 3-halo-1,2,4-triazines **5** and anilines **6** bearing a chiral oxazoline unit (Scheme 1, route B). Our ongoing research on nucleophilic substitution of 1,2,4-triazines revealed that 3,3′-dichloro-5,5′-bi-1,2,4-triazine easily undergoes nucleophilic displacement of chlorines with primary and secondary alkylamines.[19] Thus application of 3-halo-1,2,4-triazines **5** to reaction with (oxazol-2-yl)anilines **6** should provide the expected ligands **9**.

5b. Thus, the bromination reaction was carried out in boiling dichloromethane using 1.5 equiv of $POBr_3$ in the presence of *N*,*N*-dimethylaniline. After 1 h of heating 3-bromo-5,6-diphenyl-1,2,4-triazine (**5b**) was formed in 72% yield. Addition of a larger amount of $POBr_3$ or extension of time did not increase the yield of the reaction.

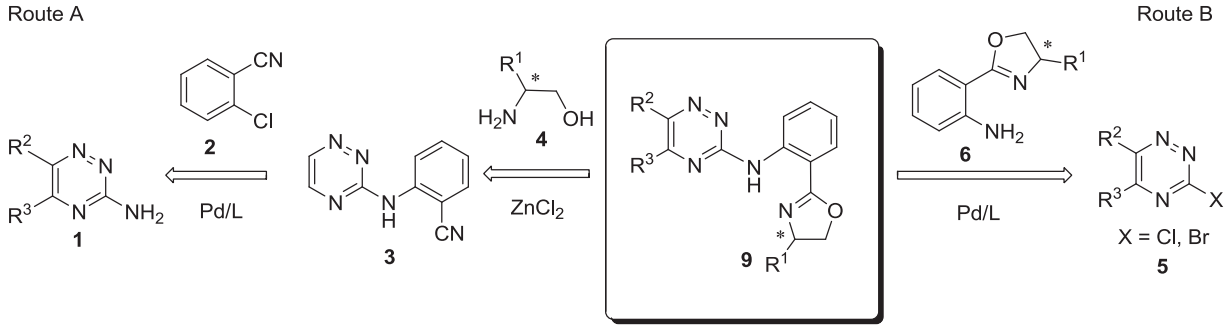
High reactivity of 3-bromo-5,6-diphenyl-1,2,4-triazine (**5b**) in aromatic nucleophilic substitution was proved in reactions with some aliphatic amines **10a**–**c**. Reactions carried out in the presence of potassium carbonate gave the appropriate products of substitution **11a**–**c** in good or excellent yield (Scheme 2).



Scheme 2. Reaction of 3-bromo-5,6-diphenyl-1,2,4-triazine (**5b**) with pyrrolidine (**10a**), ethanolamine (**10b**) and *p*-amino-benzylamine (**10c**).

However, for the reaction of 3-halo-1,2,4-triazines **5** with aromatic amines such as **6** application of Buchwald–Hartwig Pd-catalysis was necessary. When these amines were reacted in typical S_NAr conditions no products were formed. First, we studied the cross-coupling reaction of **5a**, **b** with some simple aromatic amines such as aniline and several heterocyclic amines to optimize the cross-coupling conditions (Table 1).

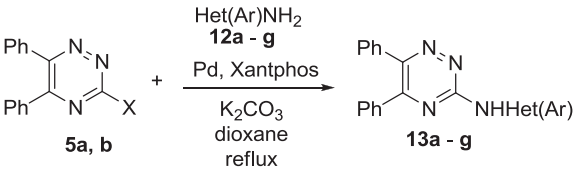
Amination of 3-choro-5,6-diphenyl-1,2,4-triazine (**5a**) with aniline (**12a**), and with three isomeric aminopyridines **12b**–**d** or aminopyrazine (**12e**) using $Pd(OAc)_2$ as the palladium source and Xantphos (Pd/L 10/20 mol %) resulted in the formation of the

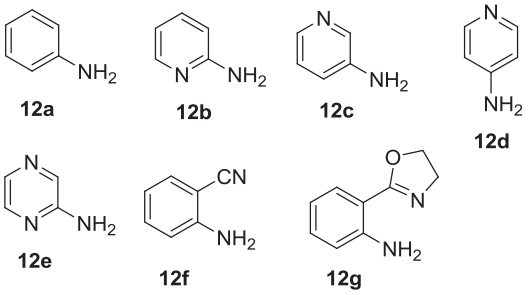


Scheme 1. Two possible synthetic strategies to chiral ligands **9**.

Initially, we considered using 3-chloro-5,6-diphenyl-1,2,4-triazine (**5a**). The latter can be easily prepared according to a known procedure by refluxing 3-hydroxy-1,2,4-triazine in $POCl_3$.[20] Since bromine is a better leaving group in cross-coupling reactions catalysed by palladium we decided to synthesise 3-bromo-5,6-diphenyl-1,2,4-triazine (**5b**). Published synthesis of analogue, 3-bromo-5-phenyl-1,2,4-triazine was afforded by melting 3-hydroxy-5-phenyl-1,2,4-triazine with $POBr_3$, which is a solid.[21] Application of this method to the synthesis of **5b** appeared inconvenient and not effective. To make the bromination reaction more practicable we were looking for a solvent in which both 3-hydroxy-1,2,4-triazine and phosphorus oxybromide are soluble. We found out that benzene or dichloromethane dissolves both the reagents and can be useful in synthesis of desired products **13a**–**e** in 47–83% yield (Table 1, entries 1–5). Palladium acetate and Pd_2dba_3 appeared not active in amination of **5a**, **b** with aminobenzonitrile (**12f**). No product was detected after the reaction. Amination of chlorotriazine **5a** with achiral 2-(4,5-dihydro-1,3-oxazol-2-yl)aniline (**12g**) was also examined. The expected product **13g** was obtained in a small amount (9%) when $Pd(OAc)_2$ was used as the palladium source (Table 1, entry 9). Use of Pd_2dba_3 instead of palladium acetate gave the coupling product **13g** in 36% yield (Table 1, entry 10). When 3-bromo-5,6-diphenyl-1,2,4-triazine (**5b**) was chosen as the coupling partner and subjected to reaction with **12g** in the presence of Pd_2dba_3 (10 mol %), Xantphos (20 mol %) and K_2CO_3 in boiling dioxane N-arylation product **13g** was isolated in 68% yield (Table 1, entry 11).

Table 1
Optimization of Buchwald–Hartwig amination reaction conditions of **5a**–**b** with aromatic and heteroaromatic amines **12a**–**g**

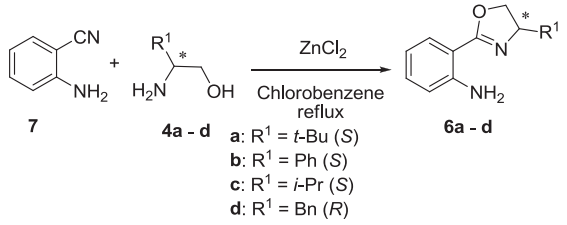




Entry	Amine	X	Pd	Product	Yield (%)
1	**12a**	Cl	$Pd(OAc)_2$	**13a**	68
2	**12b**	Cl	$Pd(OAc)_2$	**13b**	58
3	**12c**	Cl	$Pd(OAc)_2$	**13c**	47
4	**12d**	Cl	$Pd(OAc)_2$	**13d**	83
5	**12e**	Cl	$Pd(OAc)_2$	**13e**	75
6	**12f**	Cl	$Pd(OAc)_2$	—	—
7	**12f**	Cl	Pd_2dba_3	—	—
8	**12f**	Br	Pd_2dba_3	—	—
9	**12g**	Cl	$Pd(OAc)_2$	**13g**	9
10	**12g**	Cl	Pd_2dba_3	**13g**	36
11	**12g**	Br	Pd_2dba_3	**13g**	68

Our protocol of synthesis of 3-arylamino- and 3-heteroarylamino- derivatives of 1,2,4-triazine utilizes easily obtained 3-halo-1,2,4-triazines as the starting material. Such compounds were not tested in Buchwald–Hartwig amination previously. In comparison with the amination of 3-methylsulfanyl-1,2,4-triazine[22] published by Routier our methodology is simpler, and works for less active heteroaromatic amines and sterically hindered aniline **12g**. Routier's desulfurative procedure is limited to simple aliphatic amines and anilines without a substituent in *ortho* position. The methylsulfanyl group in 1,2,4-triazine is active in Buchwald–Hartwig amination under microwave irradiation only in the presence of a complex catalytic system.

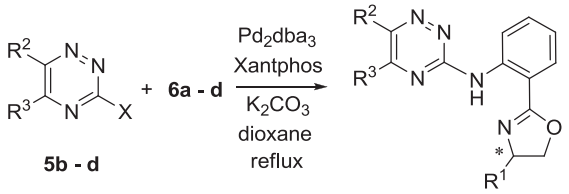
A reasonable yield of Pd-coupling between **5b** and **12g** persuaded us to adopt the optimized conditions described above to the two-step synthesis of the titled ligand class **9** according to route B depicted in Scheme 1. The synthesis of ligands began with the preparation of enantiopure 2-(*o*-aminophenyl)oxazolines **6a**–**d** by condensation of chiral amino alcohols **4a**–**d** with 2-aminobenzonitrile in the presence of $ZnCl_2$ in boiling chlorobenzene (Scheme 3).[23]



Scheme 3. Synthesis of enantiopure 2-(*o*-aminophenyl)oxazolines **6a**–**d**.

When reaction of 2-aminobenzonitrile with *tert*-leucinol was carried out according to a literature procedure[23a] in the presence of a catalytic amount (20 mol %) of $ZnCl_2$ the substrate was consumed after 5 days and the product **6a** was formed in 74% yield. The reaction proceeded faster when three-fold excess of $ZnCl_2$ was used. In these modified conditions, product **6a** was obtained in 99% yield after heating for 24 h. Similarly, oxazolylaniline **6b** was formed in 73% and 87% yield when 20 mol % or excess of $ZnCl_2$ was used. Condensations of valinol and phenylalaninol with 2-aminobenzonitrile were carried out using excess of $ZnCl_2$ and yielded the required (*o*-aminophenyl)oxazolines **6c** and **6d** in 70 and 72% yield, respectively.

Next, we conducted cross-coupling reactions of oxazolylanilines **6a**–**d** with 3-halo-1,2,4-triazines **5b**–**d** using the optimised conditions (Scheme 4, Table 2).



5b: $R^2 = R^3$ = Ph, X = Br
5c: R^2 = H, R^3 = Ph, X = Br
5d: R^2 = H, R^3 = *t*-Bu, X = Cl

Scheme 4. Synthesis of chiral ligands **9a**–**k**.

Table 2
Synthesis of chiral ligands **9a**–**k**

	Ligand	R^1	R^2	R^3	Yield (%)
1	**9a**[a]	*t*-Bu	Ph	Ph	42 (*S*)
2	**9b**	Ph	Ph	Ph	54 (*S*)
3	**9c**	*i*-Pr	Ph	Ph	68 (*S*)
4	**9d**	Bn	Ph	Ph	43 (*R*)
5	**9e**	*t*-Bu	H	Ph	28 (*S*)
6	**9f**	Ph	H	Ph	56 (*S*)
7	**9g**	*i*-Pr	H	Ph	54 (*S*)
8	**9h**	*t*-Bu	H	*t*-Bu	35 (*S*)
9	**9i**	Ph	H	*t*-Bu	49 (*S*)
10	**9j**	*i*-Pr	H	*t*-Bu	70 (*S*)
11	**9k**	Bn	H	*t*-Bu	60 (*R*)

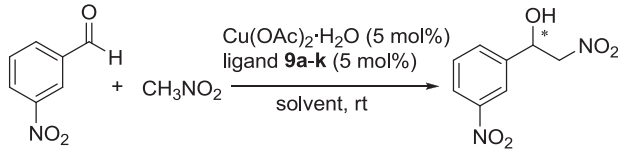
[a] The synthesis of ligand **9a** was presented previously.[24]

Thus, the Buchwald–Hartwig aryl aminations between **5b**–**d** and **6a**–**d** were carried out in boiling dioxane using K_2CO_3 as the base, Pd_2dba_3 (10 mol %) as the palladium source and Xantphos (20 mol %) as the ligand. The amination required 24 h reaction time to get complete consumption of 3-halo-1,2,4-triazines **5b**–**d**. After this time, ligands **9a**–**k** were obtained in 28–70% yield (Scheme 4, Table 2).

2.2. Enantioselective Henry reactions

With the enantiopure oxazoline ligands **9a**–**k** in hand, we examined their asymmetric induction properties in the Cu-catalyzed enantioselective Henry reaction between 3-nitrobenzaldehyde (**14a**) and nitromethane (**15**) in the presence of $Cu(OAc)_2 \cdot H_2O$, which was already known as a very good catalyst for the enantioselective nitroaldol reaction in the absence of any base. The results are summarized in Table 3. All reactions were performed at room temperature in isopropanol to afford the β-nitro alcohol **16a** in good yields of 57–95% and enantioselectivity 24–51%. Considering the relationship between the structure of the tested ligands **9a**–**k** and the enantiopurity of the obtained β-nitro alcohol **16a**, it is evident that presence of phenyl group in the oxazoline ring of ligands results in higher enantioselectivity (Table 3, entries 2, 6 and 9).

Table 3
Screening of ligands **9a**–**k**[a]



14a 15 16a

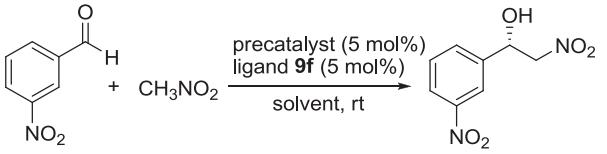
	Ligand	R^1	R^2	R^3	Yield[b] (%)	ee[c] (%)
1	**9a**	*t*-Bu	Ph	Ph	68	27 (*S*)
2	**9b**	Ph	Ph	Ph	76	40 (*S*)
3	**9c**	*i*-Pr	Ph	Ph	85	34 (*S*)
4	**9d**	Bn	Ph	Ph	87	25 (*R*)
5	**9e**	*t*-Bu	H	Ph	82	31 (*S*)
6	**9f**	Ph	H	Ph	95	46 (*S*)
7	**9g**	*i*-Pr	H	Ph	95	35 (*S*)
8	**9h**	*t*-Bu	H	*t*-Bu	57	24 (*S*)
9	**9i**	Ph	H	*t*-Bu	73	51 (*S*)
10	**9j**	*i*-Pr	H	*t*-Bu	71	33 (*S*)
11	**9k**	Bn	H	*t*-Bu	70	26 (*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 column. The absolute configuration was assigned by comparing their specific rotations or the HPLC elution order with data from the literature.[3e]

This is probably due to possible favourable π–π interaction between aldehyde and phenyl group in the oxazoline moiety. The lowest asymmetric induction was achieved when ligands with bulky *tert*-butyl group **9a**, **9e** and **9h** (Table 3, entries 1, 5 and 8) and flexible benzyl group **9d** and **9k** were used (Table 3, entries 4 and 11). The results obtained indicate that the nature of substituents in positions 5 and 6 of the 1,2,4-triazine ring does not affect the enantioselective outcome of the reaction. On the other hand, the substituents in 1,2,4-triazine strongly influence a chemical yield of the investigated reaction. The highest yield of β-nitro alcohol **16a** was observed in reactions catalyzed by complexes of ligands **9e**–**g** possessing a phenyl substituent in position 5 of the 1,2,4-triazine ring (Table 3, entries 5–7). Application of ligands **9a**–**d** with two phenyl rings in 1,2,4-triazine and ligands **9h**–**k** with a *tert*-butyl substituent in position 5 of 1,2,4-triazine afforded product with significantly lower yield (Table 3, entries 1–4 and 8–11). The (*S*)-enriched products were obtained by using the (*S*)-configured ligands (Table 3, entries 1–3 and 5–10) while ligands **9d** and **9k** with *R* configuration of stereogenic centre gave *R*-enriched β-nitro alcohols (Table 3, entries 4 and 11).

In the subsequent studies, the reaction parameters, including metal salts, solvent and catalyst loadings, were optimized. To determine the optimal conditions the asymmetric Henry reaction of 3-nitrobenzaldehyde (**14a**) with nitromethane (**15**) in the presence of ligand **9f** was tested (Table 4). A remarkable effect of the counterions on the yield and enentioselectivity was observed. Among the copper precatalysts, $Cu(OAc)_2 \cdot H_2O$, $Cu(OAc)_2$ and copper(I) thiopheno-2-carboxylate, provided the best results (Table 4, entries 1, 6 and 7). The application of $CuCl_2$ yielded no product. Next, the influence of solvent was investigated. Several protic and aprotic solvents were tested. It was observed that the type of solvent had a significant effect on both the chemical yield and enantioselectivity of the Henry products (Table 4, entries 1–4). 2-Propanol was found to be the best solvent for the reaction. Running the reaction in ethanol gave the product in 82% yield and 41% ee, while THF resulted in only 20% ee. When the reaction was carried out in a non-coordinating solvent such as dichloromethane the yield dramatically dropped to 10%. It is possible that 2-propanol coordinates the copper metal, and this process might enhance the yield and enantioselectivity. Shortening the reaction time to 40 h

Table 4
Optimization of reaction conditions[a]



14a 15 16a

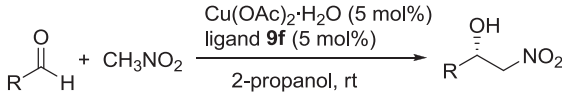
	Solvent	Precatalyst	Yield[b] (%)	ee[c] (%)
1	*i*-PrOH	$Cu(OAc)_2 \cdot H_2O$	95	46 (*S*)
2	THF	$Cu(OAc)_2 \cdot H_2O$	82	20 (*S*)
3	CH_2Cl_2	$Cu(OAc)_2 \cdot H_2O$	10	—
4	EtOH	$Cu(OAc)_2 \cdot H_2O$	82	37 (*S*)
5	*i*-PrOH	$CuCl_2$	0	—
6	*i*-PrOH	$Cu(OAc)_2$	82	41 (*S*)
7	*i*-PrOH	Copper(I) thiopheno-2-carboxylate	91	39 (*S*)
8	*i*-PrOH	$Cu(OAc)_2 \cdot H_2O$	77[d]	34 (*S*)
9	*i*-PrOH	$Cu(OAc)_2 \cdot H_2O$	83[e]	41 (*S*)

[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 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.[3e]
[d] Reaction was carried out for 40 h.
[e] Reaction was carried out in the presence of 3 mol % of ligand and 3 mol % of $Cu(OAc)_2 \cdot H_2O$.

results in reduction of efficiency and enantioselectivity to 77 and 34%, respectively (Table 4, entry 8). Finally, it was found that the reaction gave slightly decreased yield and enantiopurity of product when the catalyst loading was lowered to 3 mol % (Table 4, entry 9).

After determining the best conditions, the scope and limitation of the substrates were investigated. A variety of aldehydes were employed as substrates to afford the corresponding nitroaldol products with varied yield and enantioselectivity. The results are presented in Table 5. Aldehydes **14a**, **14c**–**f** and **14h** possessing

Table 5
Scope of aldehydes in the catalytic enantioselective Henry reaction[a]



14a – r 15 16a – r

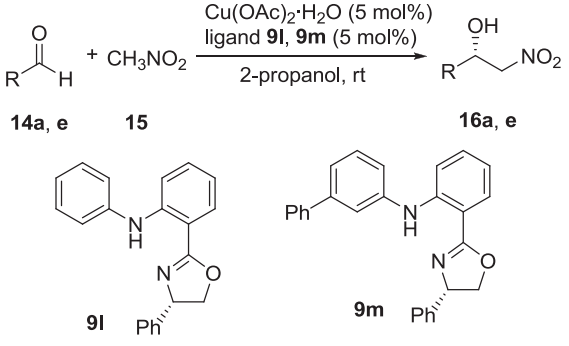
	R	Aldehyde	Product	Yield[b] (%)	ee[c] (%)
1	3-$NO_2C_6H_4$	**14a**	**16a**	95	46 (*S*)
2	Ph	**14b**	**16b**	60	52 (*S*)
3	2-$NO_2C_6H_4$	**14c**	**16c**	90	69 (*S*)
4	4-$NO_2C_6H_4$	**14d**	**16d**	82	46 (*S*)
5	2-ClC_6H_4	**14e**	**16e**	87	75 (*S*)
6	3-ClC_6H_4	**14f**	**14f**	65	58 (*S*)
7	4-ClC_6H_4	**14g**	**16g**	0	—
8	2-BrC_6H_4	**14h**	**16h**	76	82 (*S*)
9	2-MeC_6H_4	**14i**	**16i**	47	52 (*S*)
10	3-MeC_6H_4	**14j**	**16j**	59	48 (*S*)
11	4-MeC_6H_4	**14k**	**16k**	47	43 (*S*)
12	2-$MeOC_6H_4$	**14l**	**16l**	20	67 (*S*)
13	3-$MeOC_6H_4$	**14m**	**16m**	56	48 (*S*)
14	4-$MeOC_6H_4$	**14n**	**16n**	Traces	—
15	3,4-$(MeO)_2C_6H_4$	**14o**	**16o**	16	35 (*S*)
16	1-Naphthyl	**14p**	**16p**	41	50 (*S*)
17	$PhCH_2CH_2$	**14q**	**16q**	13	55 (*S*)
18	$CH_3(CH_2)_3$	**14r**	**16r**	20	56 (*S*)

[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.[3e, f, 5a, 25]

electron-withdrawing groups in the phenyl ring formed the Henry adduct in higher yield than benzaldehyde (Table 5, entries 1, 3–6 and 8). Conversely, the reactions of aldehydes with electron-donating substituents afforded the appropriate products **16i**–**o** in lower chemical yields (Table 5, entries 9–15). Position of chlorine substituent in the three positional isomers of chlorobenzaldehyde **14e**–**g** has a remarkable influence on the yield of the β-nitro alcohols (Table 5, entries 5–7). 2-Chlorobenzaldehyde gave the product in the highest yield among them. It is interesting to note that in the reaction of 4-chlorobenzaldehyde, no product was obtained. Only traces of product **16n** were detected in the reaction of 4-methoxybenzaldehyde, while 2- and 3-methoxybenzaldehydes gave the appropriate products in better yield (Table 5, entries 12–14). Decreased yield was also observed for 4-nitrobenzaldehyde in comparison to 2- and 3-nitrobenzaldehydes (Table 5, entries 1, 3 and 4). In addition, the position of the substituent plays a crucial role in induction of enantioselectivity. Aromatic aldehydes substituted in the *ortho* position produced the Henry adducts in higher enantioselectivity (Table 5, entries 3, 5, 8, 9 and 12) than those with *para* (Table 5, entries 4, 11 and 14) or *meta* (Table 5, entries 1, 6, 10 and 13) substituents. Electronic properties of substituents on the aromatic ring had a slight influence on the enantioselectivity. When aliphatic aldehydes **14q** and **14r** were chosen as substrates the reaction was much slower due to the electronic and steric effect of the sp^3-hybridized α-carbon atom (Table 5, entries 17 and 18).

To examine the role of the 1,2,4-triazine moiety on the catalytic efficiency, we designed analogous ligands **9l** and **9m** for control experiments. Comparison studies using these ligands revealed that the presence of the 1,2,4-triazine ring in the ligand structure is crucial for the reaction efficiency and enantioselectivity (Table 6). Product **16a** was obtained in significantly lower yield and ee in reactions catalyzed by ligands **9l** and **9m** (Table 6, entries 1 and 2). Only traces of Henry adduct **16e** were detected when 2-chlorobenzaldehyde (**14e**) was subjected to addition of nitromethane in the presence of catalyst derived from **9m** (Table 6, entry 3). Utility of triazine ligand **9f** led to product **16e** in 87% yield and 75% ee.

Table 6
The Henry reaction in the presence of ligands **9l** and **9m**[a]



	Ligand	R	Aldehyde	Product	Yield[b] (%)	ee[c] (%)
1	**9l**	3-$NO_2C_6H_4$	**14a**	**16a**	21	27 (*S*)
2	**9m**	3-$NO_2C_6H_4$	**14a**	**16a**	44	33 (*S*)
3	**9m**	2-ClC_6H_4	**14e**	**16e**	Traces	—

[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 column. The absolute configuration was assigned by comparing their specific rotations or the HPLC elution order with data from the literature.[3e]

3. Conclusion

In conclusion, we have demonstrated the synthesis and application of new chiral oxazoline ligands incorporating a 1,2,4-triazine ring to asymmetric nitroaldol reactions. The enantioselectivity was controlled by the substituents on the oxazoline ring. It was found that the best chiral induction was achieved by ligand **9f** possessing phenyl group in the oxazoline ring. Using this ligand high yields (up to 95%) and moderate and good enantioselectivities (up to 82%) were obtained for both aromatic and aliphatic aldehydes. It has been proven that substituents on the 1,2,4-triazine ring strongly affected reaction rate of nitromethane addition to 3-nitrobenzaldehyde. Investigation of the detailed reaction mechanism is currently in progress.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were determined at 400 and 100 MHz, respectively, with a Varian Gemini spectrometer. Chemical shifts (δ) were 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 LTQ Orbitrap Velos (Thermo Scientific) spectrometer. Infrared spectra were obtained by using a Magna FTIR—760 Nicolet apparatus. Elemental analyses were recorded with a Perkin–Elmer 2400-CHN 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 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-5,6-diphenyl-1,2,4-triazine[20] (**5a**), 3-bromo-5-phenyl-1,2,4-triazine[21] (**5b**) and 3-chloro-5-*tert*-butyl-1,2,4-triazine[26] (**5e**) were synthesised according to literature procedures.

4.2. Synthesis of 3-bromo-5,6-diphenyl-1,2,4-triazine 5b

5,6-Diphenyl-3-hydroxy-1,2,4-triazine (2 g, 8.0 mmol) was dissolved in dichloromethane (32 mL) and solution of phosphorus oxybromide (3.5 g, 12.0 mmol) in dichloromethane (5 mL) was added dropwise followed by addition of *N*,*N*-dimethylaniline (1.1 mL, 8.8 mmol). The reaction mixture was refluxed for 1 h, then the solvent was removed by distillation and the residue was poured into iced-water. The formed precipitate was filtered of and the product was purified by silica gel column chromatography using hexanes/EtOAc (5:1) to produce **5b** as a yellow solid, yield 72% (1.8 g). Mp 154–155 °C. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.58–7.32 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.2, 157.0, 154.9, 134.6, 134.3, 131.9, 130.5, 130.3, 129.7, 129.2, 129.0. Anal. Calcd for $C_{15}H_{10}BrN_3$ (311.01): C, 57.71; H, 3.23; N, 13.46; found: C, 57.65; H, 3.13; N, 13.46.

4.3. General procedure for the reaction of 3-bromo-5,6-diphenyl-1,2,4-triazine (5b) with amines 11a–c

3-Bromo-5,6-diphenyl-1,2,4-triazine (**5b**) (100 mg, 0.32 mmol), amine **10a**–**c** (0.64 mmol) and K_2CO_3 (132 mg, 0.96 mmol) were refluxed in dioxane (5 mL) until the triazine substrate was consumed (TLC control). The mixture was filtered off and the products **11a**–**c** were purified as described below.

*4.3.1. 5,6-Diphenyl-3-(pyrrolidin-1-yl)-1,2,4-triazine (**11a**).* This compound was prepared according to the General Procedure and

purified by column chromatography (CH_2Cl_2/acetone 100:1) and recrystallized from ethanol to give a yellow solid (89 mg, 92% yield). Mp 187–188 °C. IR (KBr) ν_{max}: 3055, 2976, 2946, 2864, 1540, 1477 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.53–7.52 (m, 1H), 7.51–7.50 (m, 1H), 7.45–7.42 (m, 2H), 7.39–7.36 (m, 1H), 7.32–7.31 (m, 1H), 7.31–7.27 (m, 4H), 3.40 (br s, 4H), 2.07 (br s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.3, 156.0, 147.8, 136.9, 136.7, 129.9, 129.6, 129.1, 128.1, 127.9, 46.5, 25.4. Anal. Calcd for $C_{19}H_{18}N_4$ (302.37): C, 75.47; H, 6.00; N, 18.53; found: C, 75.36; H, 6.06; N, 18.43.

*4.3.2. 2-(5,6-Diphenyl-1,2,4-triazin-3-ylamino)ethanol (**11b**).* This compound was prepared according to the General Procedure and purified by column chromatography (CH_2Cl_2/MeOH 20:1) and recrystallized from ethanol to give a yellow solid (85 mg, 91% yield). Mp 162–164 °C. IR (KBr) ν_{max}: 3423, 3255, 3083, 2933, 1595, 1524 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ: 7.83 (br s, 1H), 7.42–7.33 (m, 10H), 4.74 (t, J=5.2 Hz, 1H), 3.63–3.60 (m, 2H), 3.53 (br s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 159.1, 157.8, 155.3, 136.9, 136.8, 131.2, 130.1, 129.7, 129.2, 129.1, 60.2, 43.7. Anal. Calcd for $C_{17}H_{16}N_4O\cdot 1/4H_2O$ (296.84): C, 68.79; H, 5.60; N, 18.87; found: C, 68.77; H, 5.41; N, 18.85.

*4.3.3. N-(4-Aminobenzyl)-5,6-diphenyl-1,2,4-triazin-3-amine (**11c**).* This compound was prepared according to the General Procedure. After filtration the product precipitated from dioxane was filtered of and washed with dioxane. Yield 79% (89 mg). Mp 196–197 °C. IR (KBr) ν_{max}: 3460, 3373, 3228, 3069, 2995, 1595, 1519 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ: 8.30 (br s, 1H), 7.41–7.34 (m, 10H), 7.07 (d, J=8.4 Hz, 2H), 6.51 (d, J=8.4 Hz, 2H), 4.93 (s, 2H), 4.24 (br s, 2H). ^{13}C NMR (100 MHz, CF_3COOD–benzene) δ: 168.3, 152.3, 149.5, 138.8, 134.9, 133.3, 132.0, 131.5, 131.0, 130.2, 129.3, 129.1, 128.7, 128.2, 128.0, 44.8. Anal. Calcd for $C_{22}H_{19}N_5$ (353.42): C, 74.77; H, 5.42; N, 19.82; found: C, 74.54; H, 5.52; N, 19.59.

4.4. General procedure for the Buchwald–Hartwig palladium amination of 3-halo-5,6-diphenyl-1,2,4-triazines 5a and 5b

Method A. A two-necked flask flushed with argon was charged with anhydrous dioxane (4 mL) and Xantphos (57.8 mg, 20 mol %). After degassing, $Pd(OAc)_2$ (11.2 mg, 10 mol %) was added and the mixture was stirred under argon for 15 min at room temperature to generate the catalyst. In a second flask, 3-chloro-5,6-diphenyl-1,2,4-triazine (134 mg, 0.5 mmol), appropriate heteroamine (0.55 mmol), K_2CO_3 (1.38 g, 10 mmol) and dioxane (5 mL) were placed. The solution of generated catalyst was transferred and the resulting mixture was subsequently heated at reflux under argon until 3-chloro-5,6-diphenyl-1,2,4-triazine was consumed (TLC). After cooling, the residue was filtered off through Celite and the product was purified by column chromatography.

Method B. 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 %), heteroarylamine (0.6 mmol), 3-halo-5,6-diphenyl-1,2,4-triazine **5a** or **5b** (0.5 mmol) and K_2CO_3 (1.38 g, 10 mmol). Then, the flask was evacuated and backfilled with argon. Dioxane (10 mL) was added trough the septum. The mixture was refluxed until the 3-halo-5,6-diphenyl-1,2,4-triazine disappeared (TLC). After cooling, the solid material was filtered off and washed with CH_2Cl_2. The solvent was evaporated, and the resulting crude product was purified by column chromatography.

*4.4.1. 5,6-Diphenyl-3-phenylamino-1,2,4-triazine (**13a**).* Compound **13a** was prepared from aniline according to Method A as a yellow solid (yield 68%, 110 mg). Mp 225–226 °C. (Lit.[27] mp 230 °C). ^1H NMR (400 MHz, DMSO-d_6) δ: 10.34 (s, 1H), 7.85 (d, J=7.6 Hz, 1H), 7.50–7.34 (m, 13H), 7.03 (t, J=7.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 185.12, 181.03, 175.7, 168.7, 158.0, 147.9, 137.9, 135.9, 135.6, 130.2, 129.4, 128.9, 128.2, 128.1, 118.1, 113.1.

*4.4.2. 5,6-Diphenyl-3-[(pyridin-2-yl)amino]-1,2,4-triazine (**13b**).* Compound **13b** was prepared from 2-aminopyridine according to Method A as a yellow solid (yield 58%, 94 mg). Mp 138–139 °C. IR (KBr) ν_{max}: 3217, 2993, 1590, 1508 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ: 10.65 (s, 1H), 8.40 (ddd, J=0.8, 1.6, 4.8 Hz, 1H), 8.29 (d, J=8.4 Hz, 1H), 7.87 (ddd, J=2.0, 7.2, 8.4 Hz, 1H), 7.56–7.41 (m, 10H), 7.11 (ddd, J=0.8, 4.8, 7.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.1, 158.1, 155.9, 152.4, 150.9, 148.1, 137.9, 135.9, 135.7, 130.3, 129.5, 129.1, 128.6, 128.3, 118.2, 113.2. Anal. Calcd for $C_{20}H_{15}N_5$ (325.13): C, 73.83; H, 4.65; N, 21.52; found C, 73.59; H, 4.63; N, 21.39.

*4.4.3. 5,6-Diphenyl-3-[(pyridin-3-yl)amino]-1,2,4-triazine (**13c**).* Compound **13c** was prepared from 3-aminopyridine according to Method A as a yellow solid (yield 47%, 76 mg). Mp 202–203 °C. IR (KBr) ν_{max}: 3255, 3057, 3023, 2912, 1616, 1518 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ: 10.54 (s, 1H), 9.0 (d, J=2.4 Hz, 1H), 8.30 (ddd, J=1.6, 2.4, 8.4 Hz, 1H), 8.24 (dd, J=1.2, 4.8 Hz, 1H), 7.51–7.37 (m, 11H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 158.6, 156.1, 150.6, 143.1, 141.1, 136.4, 135.9, 135.8, 130.3, 129.4, 129.0, 128.5, 128.3, 128.2, 125.9, 123.5. Anal. Calcd for $C_{20}H_{15}N_5$ (325.13): C, 73.83; H, 4.65; N, 21.52; found C, 73.82; H, 4.69; N, 21.42.

*4.4.4. 5,6-Diphenyl-3-[(pyridin-4-yl)amino]-1,2,4-triazine (**13d**).* Compound **13d** was prepared from 4-aminopyridine according to Method A as a yellow solid (yield 83%, 135 mg). Mp 235–236 °C. IR (KBr) ν_{max}: 3263, 3032, 2923, 1597, 1509 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ: 10.83 (s, 1H), 8.48 (d, J=6.2 Hz, 2H), 7.89 (d, J=6.2 Hz, 1H), 7.57–7.42 (m, 10H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 159.4, 157.1, 152.2, 151.1, 147.3, 136.7, 136.5, 131.4, 130.4, 130.0, 129.6, 129.3, 129.2, 113.8. Anal. Calcd for $C_{20}H_{15}N_5\cdot 1/4H_2O$ (329.63): C, 72.82; H, 4.73; N, 21.23; found C, 72.96; H, 4.85; N, 21.28.

*4.4.5. 5,6-Diphenyl-3-[(pyrazinyl)amino]-1,2,4-triazine (**13e**).* Compound **13e** was prepared from aminopyrazine according to Method A as a yellow solid (yield 75%, 122 mg). Mp 215–216 °C. IR (KBr) ν_{max}: 3214, 3058, 1571, 1510 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ: 11.05 (s, 1H), 9.49 (d, J=1.3 Hz, 1H), 8.41 (dd, J=1.5, 2.4 Hz, 1H), 8.30 (d, J=2.6 Hz, 1H), 7.52–7.38 (m, 10H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 158.7, 157.1, 152.5, 150.3, 143.4, 139.2, 137.2, 136.7, 136.5, 131.4, 130.4, 130.0, 129.7, 129.3. Anal. Calcd for $C_{19}H_{14}N_6$ (326.13): C, 69.92; H, 4.32; N, 25.75; found C, 69.81; H, 4.26; N, 25.61.

*4.4.6. 5,6-Diphenyl-3-[2-(4,5-dihydro-1,3-oxazol-2-yl)phenyl] amino-1,2,4-triazine (**13g**).* Compound **13g** was prepared from 2-(4,5-dihydro-1,3-oxazol-2-yl)aniline (**12g**) and 3-bromo-5,6-diphenyl-1,2,4-triazine according to Method B as a yellow solid (yield 68%, 134 mg). Mp 213–214 °C. IR (KBr) ν_{max}: 2908, 1637, 1556, 1509 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 12.69 (s, 1H), 9.02 (d, J=8.6 Hz, 1H), 7.93 (dd, J=1.6, 8.0 Hz, 1H), 7.59–7.57 (m, 2H), 7.54–7.49 (m, 3H), 7.43–7.41 (m, 1H), 7.37–7.33 (m, 5H), 7.07–7.03 (m, 1H), 4.41 (t, J=8.8 Hz, 2H), 4.24 (t, J=8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.6, 158.9, 156.2, 150.9, 140.6, 136.1, 136.0, 132.3, 130.4, 129.8, 129.5, 129.2, 128.6, 128.3, 120.8, 118.9, 113.0, 66.1, 54.9. Anal. Calcd for $C_{24}H_{19}N_5O$ (393.16): C, 73.27; H, 4.87; N, 17.80; found C, 73.17; H, 4.79; N, 17.60.

4.5. General procedure for the synthesis of 2-(*o*-aminophenyl)oxazolines 6a–d

Method A. An oven dried two-necked flask was washed with argon and charged with 2-aminobenzonitrile (118 mg, 1 mmol), the

appropriate amino alcohol (1.5 mmol), 1 M solution of $ZnCl_2$ in Et_2O (0.2 mL, 0.2 mmol) and anhydrous chlorobenzene (6 mL). The mixture was stirred under reflux for 5 days. The solvent was then removed under reduced pressure and the product was purified by flash column chromatography on silica gel.

Method B. An oven dried two-necked flask was washed with argon and charged with 2-aminobenzonitrile (118 mg, 1 mmol), the appropriate amino alcohol (1.5 mmol), freshly flame dried $ZnCl_2$ (405 mg, 3 mmol) and anhydrous chlorobenzene (6 mL). The mixture was stirred under 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.

*4.5.1. 2-[(4S)-4-tert-Butyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (**6a**).* Compound **6a** was prepared from *S*-*tert*-leucinol (175 mg, 1.5 mmol) according to method A (yield 74%, 161 mg) or method B (yield 99%, 216 mg) after purification by silica gel chromatography (hexane/EtOAc, 5:1). All the physical and spectroscopic data are with agreement with the published ones.[23b]

*4.5.2. 2-[(4S)-4-Phenyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (**6b**).* Compound **6b** was prepared from *S*-phenylglycinol (205 mg, 1.5 mmol) according to method A (yield 73%, 174 mg) or method B (yield 87%, 207 mg) after purification by silica gel chromatography (hexane/EtOAc, 5:1). All the physical and spectroscopic data are with agreement with the published ones.[23b]

*4.5.3. 2-[(4S)-4-Isopropyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (**6c**).* Compound **6c** was prepared from *S*-valinol (155 mg, 1.5 mmol) according to method A (yield 73%, 149 mg) after purification by silica gel chromatography (hexane/EtOAc, 5:1). All the physical and spectroscopic data are with agreement with the published ones.[23b]

*4.5.4. 2-[(4R)-4-Benzyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (**6d**).* Compound **6d** was prepared from *R*-phenylalaninol (155 mg, 1.5 mmol) according to method A (yield 71%, 179 mg) after purification by silica gel chromatography (hexane/EtOAc, 5:1). All the physical and spectroscopic data are with agreement with the published ones.[23b]

4.6. General procedure for the preparation of ligands 9a–k, 9l and 9m

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-(4,5-dihydro-1,3-oxazol-2-yl)aniline **6a**–**d** (0.6 mmol), 3-halo-1,2,4-triazine **5b**–**d** (0.5 mmol) and K_2CO_3 (1.38 g, 10 mmol). Then, the flask was evacuated and backfilled with argon. Dioxane (10 mL) was added through the septum. 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 product was purified by column chromatography using hexanes/ethyl acetate (10:1) as eluent.

*4.6.1. 5,6-Diphenyl-3-{2-[(4S)-4-tert-butyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl}amino-1,2,4-triazine (**9a**).* The product was obtained from 3-bromo-5,6-diphenyl-1,2,4-triazine (**5b**) and 2-[(4*S*)-4-*tert*-butyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (**6a**) as a yellow solid, yield 42% (95 mg). All the physical and spectroscopic data were published by us previously.[24]

*4.6.2. 5,6-Diphenyl-3-{2-[(4S)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl}amino-1,2,4-triazine (**9b**).* The product was obtained from 3-bromo-5,6-diphenyl-1,2,4-triazine (**5b**) and 2-[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (**6b**) as a yellow solid, yield 54% (127 mg). Mp 164–165 °C. IR (KBr) ν_{max}: 3031, 1631, 1612, 1550, 1514 cm^{-1}. $[\alpha]_D^{20}$ +270.5 (*c* 0.85, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 12.64 (s, 1H), 8.94 (d, *J*=8.4 Hz, 1H), 8.03 (dd, *J*=1.6, 8.0 Hz, 1H), 7.60–7.54 (m, 3H), 7.50–7.48 (m, 2H), 7.44–7.30 (m, 11H), 7.13 (t, *J*=7.2 Hz, 1H), 5.66 (dd, *J*=8.4, 10.0 Hz, 1H), 4.87 (dd, *J*=10.0, 8.4 Hz, 1H), 4.34 (t, *J*=8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.7, 158.8, 156.1, 150.9, 142.0, 140.9, 136.1, 136.0, 132.6, 130.4, 129.8, 129.6, 129.2, 128.7, 128.6, 128.4, 128.3, 127.5, 126.4, 120.9, 119.1, 112.9, 73.2, 69.8. Anal. Calcd for $C_{30}H_{23}N_5O$ (469.54): C, 76.74; H, 4.94; N, 14.92; found C, 76.74; H, 4.98; N, 14.88.

*4.6.3. 5,6-Diphenyl-3-{2-[(4S)-4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl}amino-1,2,4-triazine (**9c**).* The product was obtained from 3-bromo-5,6-diphenyl-1,2,4-triazine (**5b**) and 2-[(4*S*)-4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (**6c**) as a yellow solid, yield 68% (148 mg). Mp 172–173 °C. IR (KBr) ν_{max}: 2958, 1630, 1551, 1519 cm^{-1}. $[\alpha]_D^{20}$ −11.9 (*c* 1.02, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 12.98 (s, 1H), 9.03 (d, *J*=8.4 Hz, 1H), 7.91 (dd, *J*=1.2, 8.0 Hz, 1H), 7.61–7.59 (m, 2H), 7.54–7.50 (m, 3H), 7.44–7.40 (m, 1H), 7.36–7.31 (m, 5H), 7.04 (t, *J*=8.0 Hz, 1H), 4.45 (t, *J*=8.4 Hz, 1H), 4.26–4.20 (m, 1H), 4.10 (t, *J*=8.4 Hz, 1H), 1.85 (m, 1H), 1.18 (d, *J*=6.6 Hz, 3H), 1.04 (d, *J*=6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.7, 159.2, 156.4, 151.2, 141.1, 136.5, 136.4, 132.7, 130.7, 130.1, 129.7, 129.6, 128.9, 128.7, 128.6, 121.0, 119.2, 113.3, 73.2, 70.0, 33.9, 19.35, 19.32. Anal. Calcd for $C_{27}H_{25}N_5O$ (435.52): C, 74.46; H, 5.79; N, 16.08; found: C, 74.38; H, 5.70; N, 15.97.

*4.6.4. 5,6-Diphenyl-3-{2-[(4R)-4-benzyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl}amino-1,2,4-triazine (**9d**).* The product was obtained from 3-bromo-5,6-diphenyl-1,2,4-triazine (**5b**) and 2-[(4*R*)-4-benzyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (**6d**) as a yellow solid, yield 43% (104 mg). Mp 181–182 °C. IR (KBr) ν_{max}: 3057, 3028, 2931, 1627, 1553, 1508 cm^{-1}. $[\alpha]_D^{20}$ −37.0 (*c* 0.96, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 12.65 (s, 1H), 9.02 (d, *J*=8.4 Hz, 1H), 7.91 (dd, *J*=8.0, 1.6 Hz, 1H), 7.59–7.54 (m, 2H), 7.53–7.50 (m, 3H), 7.46–7.43 (m, 1H), 7.37–7.31 (m, 7H), 7.27–7.24 (m, 2H), 7.20–7.16 (m, 1H), 7.07–7.03 (m, 1H), 4.80–4.72 (m, 1H), 4.39 (t, *J*=9.0 Hz, 1H), 4.14 (t, *J*=9.0 Hz, 1H), 3.28 (dd, *J*=6.0, 14.0 Hz, 1H), 2.86 (dd, *J*=7.6, 14 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.8, 159.0, 156.2, 150.9, 140.7, 137.8, 136.1, 136.1, 132.4, 130.3, 129.8, 129.4, 129.3, 129.2, 128.6, 128.5, 128.3, 126.5, 120.8, 118.9, 112.9, 70.5, 67.9, 41.8. Anal. Calcd for $C_{31}H_{25}N_5O$ (483.56): C, 77.00; H, 5.21; N, 14.48; found: C, 76.97; H, 5.23; N, 14.42.

*4.6.5. 3-{2-[(4S)-4-tert-Butyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl}amino-5-phenyl-1,2,4-triazine (**9e**).* The product was obtained from 3-bromo-5-phenyl-1,2,4-triazine (**5c**) and 2-[(4*S*)-4-*tert*-butyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (**6a**) as a yellow solid, yield 28% (53 mg). Mp 151–152 °C. IR (KBr) ν_{max}: 2965, 2903, 2868, 1641, 1525, 1507 cm^{-1}. $[\alpha]_D^{20}$ +21.3 (*c* 1.02, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ: 12.93 (s, 1H), 9.23 (s, 1H), 9.03 (d, *J*=8.4 Hz, 1H), 8.18 (dd, *J*=1.6, 7.6 Hz, 2H), 7.90 (dd, *J*=1.6, 8.0 Hz, 1H), 7.59–7.52 (m, 4H), 7.05 (dt, *J*=0.8, 7.6 Hz, 1H), 4.39–4.19 (m, 3H), 1.06 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.3, 160.4, 155.5, 140.8, 139.0, 134.0, 132.3, 132.1, 129.3, 129.1, 127.4, 120.7, 119.0, 112.9, 76.2, 67.4, 34.0, 25.9. Anal. Calcd for $C_{22}H_{23}N_5O$ (373.45): C, 70.76; H, 6.21; N, 18.75; found: C, 70.78; H, 6.19; N, 18.68.

*4.6.6. 3-{2-[(4S)-4-Phenyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl}amino-5-phenyl-1,2,4-triazine (**9f**).* The product was obtained from 3-bromo-5-phenyl-1,2,4-triazine (**5c**) and 2-[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (**6b**) as a yellow solid, yield 56% (112 mg). Mp 147–148 °C. IR (KBr) ν_{max}: 3026, 1636, 1618, 1522 cm^{-1}. $[\alpha]_D^{20}$ +321.6 (*c* 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ:

12.68 (s, 1H), 9.23 (s, 1H), 9.02 (d, J=8.4 Hz, 1H), 8.15 (dd, J=1.6, 8.0 Hz, 2H), 7.99 (dd, J=1.6, 8.0 Hz, 1H), 7.61–7.51 (m, 4H), 7.43–7.36 (m, 4H), 7.33–7.28 (m, 1H), 7.10 (dt, J=0.8, 8.0 Hz, 1H), 5.65 (dd, J=8.8, 10.0 Hz, 1H), 4.82 (dd, J=8.4, 10.0 Hz, 1H), 4.27 (t, J=8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.7, 160.5, 155.5, 142.0, 140.8, 139.2, 134.0, 132.6, 132.1, 129.6, 129.2, 128.8, 127.5, 126.4, 121.0, 119.2, 113.0, 73.2, 70.0. Anal. Calcd for $C_{24}H_{19}N_5O$ (393.44): C, 73.27; H, 4.87; N, 17.80; found: C, 73.29; H, 4.90; N, 17.64.

*4.6.7. 3-{2-[(4S)-4-Isopropyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl} amino-5-phenyl-1,2,4-triazine (**9g**).* The product was obtained from 3-bromo-5-phenyl-1,2,4-triazine (**5c**) and 2-[(4*S*)-4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (**6c**) as a yellow solid, yield 54% (98 mg). Mp 138–139 °C. IR (KBr) ν_{max}: 2957, 2895, 2872, 1638, 1508 cm^{-1}. $[\alpha]_D^{20}$ +20.2 (*c* 1.01, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.87 (s, 1H), 9.23 (s, 1H), 9.01 (d, J=8.0 Hz, 1H), 8.17 (d, J=7.2 Hz, 2H), 7.90 (dd, J=1.6, 7.6 Hz, 1H), 7.58–7.52 (m, 4H), 7.05 (dt, J=0.8, 8.4 Hz, 1H), 4.45 (dd, J=8.4, 9.6 Hz, 1H), 4.27–4.21 (m, 1H), 4.10 (t, J=8.4, Hz, 1H), 1.88–1.81 (m, 1H), 1.19 (d, J=6.4 Hz, 3H), 1.05 (d, J=6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.3, 160.4, 155.4, 140.7, 139.0, 134.0, 132.3, 132.1, 129.3, 129.1, 127.5, 120.8, 119.0, 113.0, 73.0, 69.6, 33.5, 19.0, 18.9. Anal. Calcd for $C_{21}H_{21}N_5O$ (359.42): C, 70.17; H, 5.89; N, 19.48; found: C, 70.09; H, 5.88; N, 19.48.

*4.6.8. 5-tert-Butyl-3-{2-[(4S)-4-tert-butyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl}amino-1,2,4-triazine (**9h**).* The product was obtained from 3-chloro-5-*tert*-butyl-1,2,4-triazine (**5d**) and 2-[(4*S*)-4-*tert*-butyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (**6a**) as a yellow solid, yield 35% (62 mg). Mp 127–128 °C. IR (KBr) ν_{max}: 3234, 3028, 2958, 2901, 2867, 1639, 1615, 1548 cm^{-1}. $[\alpha]_D^{20}$ −0.76 (*c* 1.02, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.72 (s, 1H), 8.98 (d, J=8.8 Hz, 1H), 8.84 (s, 1H), 7.87 (dd, J=1.6, 8.0 Hz, 1H), 7.50 (ddd, J=1.6, 7.2, 8.8 Hz, 1H), 7.02 (dt, J=0.8, 7.6 Hz, 1H), 4.37–4.33 (m, 1H), 4.25–4.17 (m, 2H), 1.38 (s, 1H), 1.02 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.6, 163.3, 159.8, 140.8, 140.1, 132.3, 129.2, 120.5, 119.0, 112.7, 76.2, 67.4, 36.6, 34.0, 28.7, 25.8. Anal. Calcd for $C_{20}H_{27}N_5O$ (353.46): C, 67.96; H, 7.70; N, 19.81; found: C, 67.79; H, 7.61; N, 19.49.

*4.6.9. 5-tert-Butyl-3-{2-[(4S)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl] phenyl}amino-1,2,4-triazine (**9i**).* The product was obtained from 3-chloro-5-*tert*-butyl-1,2,4-triazine (**5d**) and 2-[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (**6b**) as a yellow solid, yield 49% (92 mg). Mp 160–162 °C. IR (KBr) ν_{max}: 3232, 3095, 3020, 2962, 2904, 1632, 1616, 1525 cm^{-1}. $[\alpha]_D^{20}$ +238.6 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.57 (s, 1H), 8.95 (dd, J=0.6, 8.4 Hz, 1H), 8.85 (m, 1H), 7.96 (dd, J=1.6, 8.0 Hz, 1H), 7.53 (ddd, J=2.0, 7.6, 8.8 Hz, 1H), 7.41–7.34 (m, 4H), 7.31–7.29 (m, 1H), 7.06 (ddd, J=0.8, 7.6, 8.0 Hz, 1H), 5.63 (dd, J=8.6, 10.2 Hz, 1H), 4.81 (dd, J=8.6, 10.2 Hz, 1H), 4.25 (t, J=8.6 Hz, 1H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.5, 164.6, 160.0, 142.0, 140.9, 140.0, 132.5, 129.6, 128.7, 127.5, 126.3, 120.7, 119.0, 112.8, 73.1, 69.8, 36.7, 28.8. Anal. Calcd for $C_{22}H_{23}N_5O$ (373.45): C, 70.76; H, 6.21; N, 18.75; found: C, 70.54; H, 6.17; N, 18.62.

*4.6.10. 5-tert-Butyl-3-{2-[(4S)-4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl}amino-1,2,4-triazine (**9j**).* The product was obtained from 3-chloro-5-*tert*-butyl-1,2,4-triazine (**5d**) and 2-[(4*S*)-4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (**6c**) as a yellow solid, yield 70% (119 mg). Mp 89–90 °C. IR (KBr) ν_{max}: 3029, 2956, 2899, 2868, 1636, 1617, 1510 cm^{-1}. $[\alpha]_D^{20}$ −76.3 (*c* 1.01, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.68 (s, 1H), 8.95 (d, J=8.4 Hz, 1H), 8.83 (s, 1H), 7.87 (dd, J=1.7, 7.8 Hz, 1H), 7.49 (ddd, J=1.7, 7.4, 8.8 Hz, 1H), 7.01 (dt, J=0.9, 8.0 Hz, 1H), 4.43 (dd, J=8.1, 9.4 Hz, 1H), 4.22–4.15 (m, 1H), 4.06 (t, J=8.1 Hz, 1H), 1.87–1.76 (m, 1H), 1.16 (d, J=6.7, 1H), 1.01 (d, J=6.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.6, 163.4, 159.8, 140.8, 140.0, 132.2, 129.3, 120.5, 118.9, 112.8, 72.9, 69.7, 36.2, 33.6, 28.7, 19.1, 18.9. HRMS (ESI, *m*/*z*): Calcd for $C_{19}H_{25}N_5ONa$ ($[M+Na]^+$), 362.1951, found 362.1942.

*4.6.11. 5-tert-Butyl-3-{2-[(4R)-4-benzyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl}amino-1,2,4-triazine (**9k**).* The product was obtained from 3-chloro-5-*tert*-butyl-1,2,4-triazine (**5d**) and 2-[(4*R*)-4-benzyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (**6c**) as a yellow solid, yield 60% (116 mg). Mp 89–90 °C. IR (KBr) ν_{max}: 3029, 2967, 1633, 1608, 1528 cm^{-1}. $[\alpha]_D^{20}$ −12.7 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.53 (s, 1H), 8.89 (dd, J=0.4, 8.8 Hz, 1H), 7.87 (dd, J=1.6, 7.2 Hz, 1H), 7.50 (ddd, J=1.6, 7.2, 8.8 Hz, 1H), 7.31–7.28 (m, 4H), 7.25–7.21 (m, 1H), 7.02 (ddd, J=1.2, 8.0, 8.4 Hz, 1H), 4.79–4.72 (m, 1H), 4.35 (t, J=8.4 Hz, 1H), 4.11 (t, J=8.4, 1H), 3.29 (dd, J=5.4, 14.0 Hz, 1H), 2.85 (dd, J=8.0, 14.0 Hz, 1H), 1.41 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.4, 163.8, 160.1, 140.8, 139.9, 137.7, 132.2, 129.4, 129.3, 128.6, 126.6, 120.6, 118.8, 112.9, 70.4, 67.9, 41.7, 36.7, 28.8. Anal. Calcd for $C_{23}H_{25}N_5O$ (387.48): C, 71.29; H, 6.50; N, 18.07; found: C, 71.30; H, 6.43; N, 17.99.

*4.6.12. N-Phenyl-2-[(4S)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (**9l**).* The product was obtained from bromobenzene and 2-[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (**6b**) as a colourless viscous oil, yield 84% (132 mg). IR (KBr) ν_{max}: 3233, 3170, 3029, 2923, 2852, 1629, 1592, 1518 cm^{-1}. $[\alpha]_D^{20}$ +352.3 (*c* 1.9, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.51 (br s, 1H), 7.90 (dd, J=1.2, 7.6 Hz, 1H), 7.39–7.25 (m, 11H), 7.07–7.03 (m, 1H), 6.79 (ddd, J=1.2, 6.8, 8.0 Hz, 1H), 5.50 (dd, J=8.4, 10.0 Hz, 1H), 4.74 (dd, J=8.0, 10.0 Hz, 1H), 4.17 (t, J=8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.1, 146.1, 142.4, 141.3, 132.3, 130.2, 129.2, 128.7, 127.6, 126.5, 123.0, 122.1, 116.9, 113.3, 109.9, 73.2, 70.0. HRMS (ESI, *m*/*z*): calcd for $C_{21}H_{19}N_2O$ ($[M+H]^+$), 315.1492, found 315.1490.

*4.6.13. 3-{2-[(4S)-4-Phenyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl}aminobiphenyl (**9m**).* The product was obtained from 3-bromobiphenyl and 2-[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (**6b**) as a colourless viscous oil, yield 44% (85 mg). IR (KBr) ν_{max}: 3225, 3057, 3028, 2919, 2897, 1629, 1601, 1579 cm^{-1}. $[\alpha]_D^{20}$ +303.1 (*c* 0.92, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.58 (br s, 1H), 7.91 (dd, J=1.6, 8.0 Hz, 1H), 7.60–7.58 (m, 2H), 7.49 (t, J=1.6 Hz, 1H), 7.45–7.24 (m, 13H), 6.83–6.79 (m, 1H), 5.51 (dd, J=8.4, 10.0 Hz, 1H), 4.75 (dd, J=8.4, 10.0 Hz, 1H), 4.19 (t, J=8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.6, 146.1, 142.4, 142.3, 141.7, 140.9, 132.4, 130.3, 129.6, 128.8, 128.7, 127.6, 127.3, 127.1, 126.5, 121.9, 120.9, 120.8, 117.1, 113.5, 110.1, 73.2, 70.0. HRMS (ESI, *m*/*z*): calcd for $C_{27}H_{23}N_2O$ ($[M+H]^+$), 391.1805, found 391.1804.

4.7. 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 **9a**–**k** (0.025 mmol, 5 mol %) in anhydrous 2-propanol (2 mL) 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 added and the reaction was conducted at room temperature for 4 days. Then the solvent was removed under reduced pressure and the product was isolated by column chromatography. The ee values of the nitroalcohols **16a**–**r** were determined by chiral HPLC analysis. The absolute configurations of the products were assigned by comparing their specific rotations or the retention times in HPLC with literature data.[3e,25]

*4.7.1. (S)-2-Nitro-1-(3-nitrophenyl)ethanol (**16a**).* Compound **16a** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 2.5:1) to give a colourless solid (100 mg, 95% yield). $[\alpha]_D^{20}$ +20.5 (*c* 1.25, CH_2Cl_2). [Lit.[7h] $[\alpha]_D^{20}$ +36.2 (*c* 1.25, CH_2Cl_2), 81% ee]. ^{1}H 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[3e] (Chiralcel OD-H, hexane/*i*-PrOH 90:10, flow rate: 1.0 mL/min, λ=215 nm), t_{minor}=28.2, t_{major}=32.4, 46% ee.

*4.7.2. (S)-2-Nitro-1-phenylethanol (**16b**).* Compound **16b** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 7:1) to give a colourless oil (50 mg, 60% yield). $[\alpha]_D^{20}$ +23.1 (*c* 0.96, CH_2Cl_2). [Lit.[3e] $[\alpha]_D^{20}$ +40.2 (*c* 0.96, CH_2Cl_2), 98% ee]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43–7.34 (m, 5H), 5.45 (dd, J=4.0, 8.0 Hz, 1H), 4.59 (dd, J=12.0, 16.0 Hz, 1H), 4.50 (dd, J=4.0, 12.0 Hz, 1H), 2.85 (br s, 1H). HPLC[25a] (Chiralcel OD-H, hexane/*i*-PrOH 85:15, flow rate: 1.0 mL/min, λ=215 nm), t_{minor}=10.3, t_{major}=12.2, 52% ee.

*4.7.3. (S)-2-Nitro-1-(2-nitrophenyl)ethanol (**16c**).* Compound **16c** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 5:1) to give a brown solid (95 mg, 90% yield). $[\alpha]_D^{20}$ −121.9 (*c* 0.23, CH_2Cl_2). [Lit.[7h] $[\alpha]_D^{20}$ −169.4 (*c* 0.22, CH_2Cl_2), 87% ee]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08 (dd, J=1.2, 8.0 Hz, 1H), 7.95 (dd, J=1.2, 8.0 Hz, 1H), 7.77–7.73 (m, 1H), 7.58–7.54 (m, 1H), 6.08–6.04 (m, 1H), 4.87 (dd, J=2.4, 14.0 Hz, 1H), 4.55 (dd, J=8.8, 14.0 Hz, 1H), 3.14 (d, J=4.0 Hz, 1H). HPLC[25b] (Chiralcel OD-H, hexane/*i*-PrOH 90:10, flow rate: 1.0 mL/min, λ=215 nm), t_{minor}=15.9, t_{major}=17.9, 69% ee.

*4.7.4. (S)-2-Nitro-1-(4-nitrophenyl)ethanol (**16d**).* Compound **16d** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 5:1) to give a colourless solid (85 mg, 82% yield). $[\alpha]_D^{20}$ +21.0 (*c* 1.0, CH_2Cl_2). [Lit.[3e] $[\alpha]_D^{20}$ +36.1 (*c* 0.98, CH_2Cl_2), 95% ee]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.27 (d, J=8.4 Hz, 2H), 7.62 (d, J=8.4 Hz, 2H), 5.61–5.58 (m, 1H), 4.64–4.55 (m, 2H), 3.08 (d, J=4.0 Hz, 1H). HPLC[25b] (Chiralcel OD-H, hexane/*i*-PrOH 85:15, flow rate: 1.0 mL/min, λ=215 nm), t_{minor}=17.8, t_{major}=22.3, 46% ee.

*4.7.5. (S)-1-(2-Chlorophenyl)-2-nitroethanol (**16e**).* Compound **16e** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 7:1) to give a colourless oil (87 mg, 87% yield). $[\alpha]_D^{20}$ +42.8 (*c* 1.03, CH_2Cl_2). [Lit.[3e] $[\alpha]_D^{20}$ +47.7 (*c* 1.07, CH_2Cl_2), 99% ee]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (dd, J=2.0, 7.6 Hz, 1H), 7.40–7.31 (m, 3H), 5.87–5.84 (m, 1H), 4.69 (dd, J=2.4, 14.0 Hz, 1H), 4.46 (dd, J=9.6, 14.0 Hz, 1H), 2.93 (d, J=4.4 Hz, 1H). HPLC[3f] (Chiralcel OD-H, hexane/*i*-PrOH 98:2, flow rate: 1.0 mL/min, λ=215 nm), t_{minor}=25.0, t_{major}=27.2, 75% ee.

*4.7.6. (S)-1-(3-Chlorophenyl)-2-nitroethanol (**16f**).* Compound **16f** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 7:1) to give a colourless oil (65 mg, 65% yield). $[\alpha]_D^{20}$ +44.4 (*c* 0.5, CH_2Cl_2). [Lit.[3e] $[\alpha]_D^{20}$ +73.7 (*c* 0.48, CH_2Cl_2), 97% ee]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44–7.43 (m, 1H), 7.35–7.34 (m, 2H), 7.30–7.27 (m, 1H), 5.46 (dd, J=2.8, 9.2 Hz, 1H), 4.59 (dd, J=2.8, 9.2 Hz, 1H), 4.52 (dd, J=3.2, 13.6 Hz, 1H), 2.88 (br s, 1H). HPLC[3e] (Chiralcel OD-H, hexane/*i*-PrOH 90:10, flow rate: 1.0 mL/min, λ=215 nm), t_{minor}=14.1, t_{major}=17.9, 58% ee.

*4.7.7. (S)-1-(2-Bromophenyl)-2-nitroethanol (**16h**).* Compound **16h** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 8:1) to give a colourless oil (94 mg, 76% yield). $[\alpha]_D^{20}$ +38.7 (*c* 0.9, CH_2Cl_2). [Lit.[3e] $[\alpha]_D^{20}$ +46.2 (*c* 0.90, CH_2Cl_2), 98% ee]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (dd, J=1.6, 7.6 Hz, 1H), 7.57 (dd, J=1.2, 8.0 Hz, 1H), 7.41 (dt, J=0.8, 7.2 Hz, 1H), 7.23 (dt, J=1.6, 7.6 Hz, 2H), 5.83–5.79 (m, 1H), 4.69 (dd, J=1.6, 13.6 Hz, 1H), 4.44 (dd, J=9.6, 13.6 Hz, 1H), 2.94 (d, J=4.4 Hz, 1H). HPLC[3e] (Chiralcel OD-H, hexane/*i*-PrOH 90:10, flow rate: 1.0 mL/min, λ=215 nm), t_{minor}=10.6, t_{major}=11.0, 82% ee.

*4.7.8. (S)-1-(2-Methylphenyl)-2-nitroethanol (**16i**).* Compound **16i** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 10:1) to give a yellow oil (50 mg, 47% yield). $[\alpha]_D^{20}$ +28.0 (*c* 1.01, CH_2Cl_2). [Lit.[3e] $[\alpha]_D^{20}$ +52.8 (*c* 1.01, CH_2Cl_2), 99% ee]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.54–7.52 (m, 1H), 7.31–7.25 (m, 2H), 7.20–7.18 (m, 1H), 5.71–5.68 (m, 1H), 4.57 (dd, J=9.6, 13.4 Hz, 1H), 4.46 (dd, J=2.8, 13.4 Hz, 1H), 2.64 (d, J=3.6 Hz, 1H), 2.39 (s, 3H). HPLC[3e] (Chiralcel OD-H, hexane/*i*-PrOH 90:10, flow rate: 1.0 mL/min, λ=215 nm), t_{minor}=11.7, t_{major}=17.9, 52% ee.

*4.7.9. (S)-1-(3-Methylphenyl)-2-nitroethanol (**16j**).* Compound **16j** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 8:1) to give a yellow oil (54 mg, 59% yield). $[\alpha]_D^{20}$ +21.2 (*c* 0.5, CH_2Cl_2). [Lit.[3e] $[\alpha]_D^{20}$ +38.8 (*c* 0.50, CH_2Cl_2), 98% ee]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (t, J=7.6 Hz, 1H), 7.22–7.17 (m, 3H), 5.43 (dd, J=3.2, 9.6 Hz, 1H), 4.61 (dd, J=9.6, 13.6 Hz, 1H), 4.51 (dd, J=3.2, 13.6 Hz, 1H), 2.75 (br s, 1H), 2.38 (s, 3H). HPLC[3e] (Chiralcel OD-H, hexane/*i*-PrOH 90:10, flow rate: 1.0 mL/min, λ=215 nm), t_{minor}=12.0, t_{major}=13.9, 48% ee.

*4.7.10. (S)-1-(4-Methylphenyl)-2-nitroethanol (**16k**).* Compound **16k** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 5:1) to give a yellow oil (43 mg, 47% yield). $[\alpha]_D^{20}$ +10.9 (*c* 1.10, CH_2Cl_2). [Lit.[3e] $[\alpha]_D^{20}$ +24.8 (*c* 1.10, CH_2Cl_2), 98% ee]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (d, J=8.0 Hz, 2H), 7.21 (d, J=8.0 Hz, 2H), 5.43 (dd, J=2.8, 9.6 Hz, 1H), 4.61 (dd, J=9.6, 13.2 Hz, 1H), 4.50 (dd, J=2.8, 13.2 Hz, 1H), 2.69 (br s, 1H), 2.37 (s, 3H). HPLC[3e] (Chiralcel OD-H, hexane/*i*-PrOH 90:10, flow rate: 1.0 mL/min, λ=215 nm), t_{minor}=14.4, t_{major}=18.4, 43% ee.

*4.7.11. (S)-1-(2-Methoxyphenyl)-2-nitroethanol (**16l**).* Compound **16l** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 10:1) to give a yellow oil (20 mg, 20% yield). $[\alpha]_D^{20}$ +15.7 (*c* 1.05, CH_2Cl_2). [Lit.[3e] $[\alpha]_D^{20}$ +45.0 (*c* 1.05, CH_2Cl_2), 96% ee]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46–7.43 (m, 1H), 7.35–7.31 (m, 1H), 7.04–6.99 (m, 1H), 6.91 (d, J=8.4 Hz, 1H), 5.64 (dd, J=3.2, 9.2 Hz, 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), 3.12 (br s, 1H). HPLC[3e] (Chiralcel OD-H, hexane/*i*-PrOH 90:10, flow rate: 1.0 mL/min, λ=215 nm), t_{minor}=11.8, t_{major}=13.9, 67% ee.

*4.7.12. (S)-1-(3-Methoxyphenyl)-2-nitroethanol (**16m**).* Compound **16m** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 7:1) to give a yellow oil (55 mg, 56% yield). $[\alpha]_D^{20}$ +23.8 (*c* 0.6, CH_2Cl_2). [Lit.[3e] $[\alpha]_D^{20}$ +36.3 (*c* 0.60, CH_2Cl_2), 92% ee]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33–7.29 (m, 1H), 6.97–6.95 (m, 2H), 6.91–6.88 (m, 1H), 5.44 (dd, J=3.2, 9.6 Hz, 1H), 4.60 (dd, J=9.6, 13.6 Hz, 1H), 4.50 (dd, J=3.2, 13.6 Hz, 1H), 3.82 (s, 3H), 2.31 (br s, 1H). HPLC[3e] (Chiralcel OD-H, hexane/*i*-PrOH 90:10, flow rate: 1.0 mL/min, λ=215 nm), t_{minor}=23.9, t_{major}=31.5, 48% ee.

*4.7.13. (S)-1-(3,4-Dimethoxyphenyl)-2-nitroethanol (**16o**).* Compound **16o** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 2.5:1) to give a yellow oil (18 mg, 16% yield). $[\alpha]_D^{20}$ +12.5 (*c* 1.32, CH_2Cl_2). [Lit.[25a] $[\alpha]_D^{20}$ +28.1 (*c* 1.2, CH_2Cl_2), 82% ee]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.94–6.85 (m, 3H), 5.42 (dd, J=4.0, 12.0 Hz, 1H), 4.61 (dd, J=12.0, 16.0 Hz, 1H), 4.50 (dd, J=4.0, 12.0 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 2.74 (br s, 1H). HPLC25a (Chiralcel OD-H,

hexane/*i*-PrOH 85:15, flow rate: 1.0 mL/min, λ=215 nm), t_{minor}=29.0, t_{major}=38.7, 35% ee.

*4.7.14. (S)-1-(1-Naphthyl)-2-nitroethanol (**16p**).* Compound **16p** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 10:1) to give a yellow oil (44 mg, 41% yield). $[\alpha]_D^{20}$ +7.57 (*c* 1.08, CH_2Cl_2). [Lit.[3e] $[\alpha]_D^{20}$ +26.0 (*c* 1.06, CH_2Cl_2), 98% ee]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05 (d, *J*=8.8 Hz, 1H), 7.92 (d, *J*=8.8 Hz, 1H), 7.87 (d, *J*=8.4 Hz, 1H), 7.77 (d, *J*=8.8 Hz, 1H), 7.62–7.51 (m, 3H), 6.27 (dd, *J*=3.6, 8.4 Hz, 1H), 4.72–4.64 (m, 2H), 2.87 (br s, 1H). HPLC[25b] (Chiralcel OD-H, hexane/*i*-PrOH 90:10, flow rate: 1.0 mL/min, λ=215 nm), t_{minor}=18.9, t_{major}=28.1, 50% ee.

*4.7.15. (S)-1-Nitro-4-phenylbutan-2-ol (**16q**).* Compound **16q** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 5:1) to give a colourless solid (13 mg, 14% yield). $[\alpha]_D^{20}$ −8.2 (*c* 1.00, CH_2Cl_2). [Lit.[3e] $[\alpha]_D^{20}$ −14.2 (*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), 2.48 (br s, 1H), 1.92–1.75 (m, 2H). HPLC[5a] (Chiralpak AD-H, hexane/*i*-PrOH 95:5, flow rate: 0.7 mL/min, λ=215 nm), t_{minor}=28.6, t_{major}=36.5, 55% ee.

*4.7.16. (S)-1-Nitroheksan-2-ol (**16r**).* Compound **16r** was obtained according to the general procedure and purified by column chromatography (hexanes/ethyl acetate 5:1) to give a yellow oil (15 mg, 20% yield). $[\alpha]_D^{20}$ +6.0 (*c* 0.70, CH_2Cl_2). [Lit.[28] $[\alpha]_D^{20}$ +10.5 (*c* 0.70, CH_2Cl_2), 98% ee]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.44 (dd, *J*=2.8, 12.8 Hz, 1H), 4.40–4.28 (m, 2H), 2.01 (br s, 1H), 1.59–1.42 (m, 3H), 1.41–1.32 (m, 3H), 0.92 (t, *J*=6.8 Hz, 3H). HPLC[25c] (Chiralpak AD-H, hexane/*i*-PrOH 98:2, flow rate: 0.8 mL/min, λ=215 nm), t_{minor}=30.4, t_{major}=40.6, 56% ee.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.06.084. These data include MOL files and InChiKeys of the most important compounds described in this article.

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