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Chiral oxazoline ligands with two different six-membered azaheteroaromatic rings – synthesis and application in the Cu-catalyzed nitroaldol reaction

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Abstract: Synthesis and catalytic activity of chiral ligands 5,6-diphenyl-3-{3-[(4*S*/*R*)-4-R/Ar-4,5-dihydro-1,3-oxazol-2-yl]pyridin-2-yl}amino-1,2,4-triazines **2** and their analogs **3** possessing an *N*-oxide function in the pyridine ring are described. The pivotal step in the synthesis of ligands **2** is the Buchwald-Hartwig Pd-catalyzed cross-coupling reaction between 3-bromo-5,6-diphenyl-1,2,4-triazine (**7a**) and enantiopure 3-(4,5-dihydro-1,3-oxazol-2-yl)pyridin-2-amines **6a**–**d**. Aromatic nucleophilic substitution of chlorine in 3-chloro-5,6-diphenyl-1,2,4-triazine (**7b**) with 3-(4,5-dihydro-1,3-oxazol-2-yl)pyridin-2-amine 1-oxides **12** was investigated as the key reaction in the synthesis of ligands **3**. Two undesired derivatives **13** or **14**, resulting from unexpected reactions of **3**, were isolated depending on reaction conditions. Compounds **2** and **3** as well as the side products **13** and **14** were screened as chiral ligands in the copper catalyzed enatioselective nitroaldol reaction.

Keywords: asymmetric catalysis; Buchwald-Hartwig amination; chiral oxazoline ligands; enantioselective Henry reaction; 1,2,4-triazine.

Introduction

According to our interest focusing on the design, synthesis, and applications of chiral oxazoline ligands we have already described several ligands **1** which combine in their structure two heterocyclic moieties: chiral oxazoline and 1,2,4-triazine linked by an *N*-phenylamine unit (Figure 1). The ligands differ in the type of a substituent in the oxazoline ring and in the substitution mode of the 1,2,4-triazine moiety.

These ligands were applied to the copper catalyzed enantioselective nitroaldol reaction of several aromatic and aliphatic aldehydes providing products with enantiopurity up to 92% and yield up to 95% [1–3]. Thus, the ligands with the phenyl substituent in the oxazoline ring and ligands that possess the indane moiety exhibit high stereocontrolling abilities. Substitution in the 1,2,4-triazine ring has a crucial impact on chemical yield of the investigated reaction. From this point of view, the ligands having a phenyl group at the C5 position of 1,2,4-triazine are preferred. Structures of **1**-Cu complexes so far are not known, but it can be suggested on the basis of the ligand crystal structures [4] that the nitrogen atoms of oxazoline and amino groups may participate in the complexation of copper ion. Similar complexation mode of zinc was observed by Guiry [5]. In the Henry reaction, a base or counter ion is necessary to abstract the proton from nitromethane. Our catalytic system works without an external base, so the nitronate anion must be generated with the involvement a counter ion or the **1**-Cu complex plays the role of a bifunctional catalyst. As an extension of the previous work, now we report the synthesis of chiral oxazoline ligands **2** and **3** as analogs of ligands **1** where the *N*-phenylamine linkage is replaced with pyridine-2-amine or 2-aminopyridine 1-oxide moiety (Figure 2). The presence of the nitrogen atom or *N*-oxide moiety in the linkage can change electronic properties of the donating nitrogen atoms, thus having impact on the complexation and stereo-controlling abilities of ligands. They can also act as an additional internal base. On the other hand, the competition between the new electron pair donors and the nitrogen atoms of oxazoline and amino groups in complexation with copper ion can take place.

Results and discussion

The 1,2,4-triazine ring is π-electron deficient and, therefore, susceptible to nucleophilic attack [6]. Highly active

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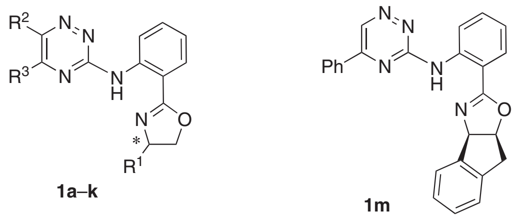


a: $R^2 = R^3 = Ph, R^1 = t\text{-}Bu\ (S)$
b: $R^2 = R^3 = Ph, R^1 = Ph\ (S)$
c: $R^2 = R^3 = Ph, R^1 = i\text{-}Pr\ (S)$
d: $R^2 = R^3 = Ph, R^1 = Bn\ (R)$
e: $R^2 = H, R^3 = Ph, R^1 = t\text{-}Bu\ (S)$
f: $R^2 = H, R^3 = Ph, R^1 = Ph\ (S)$
g: $R^2 = H, R^3 = Ph, R^1 = i\text{-}Pr\ (S)$
h: $R^2 = H, R^3 = t\text{-}Bu, R^1 = t\text{-}Bu\ (S)$
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 Previously investigated 1,2,4-triazine-oxazoline ligands.

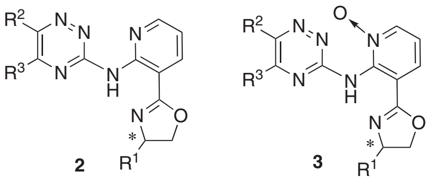
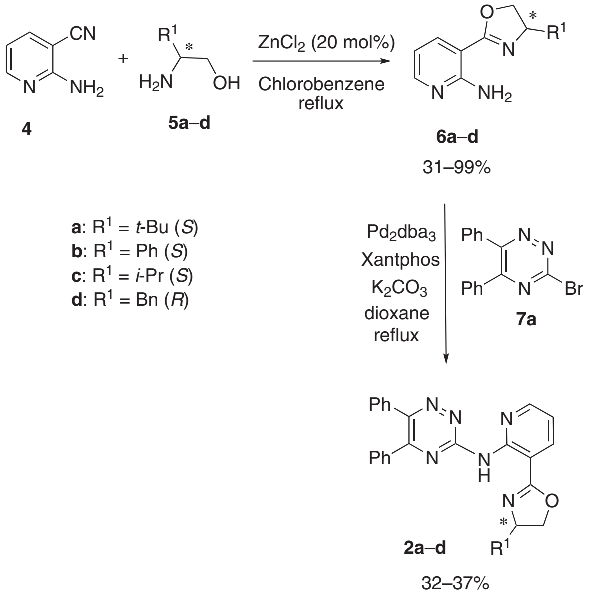


Figure 2 Chiral oxazoline ligands with six-membered azaheteroaromatic rings.

3,3′-dichloro-5,5′-bi-1,2,4-triazine undergoes displacement of chlorine atoms after few minutes of stirring with aliphatic amines or aniline in the absence of an additional base [7]. Reactions of less active 1,2,4-triazines require the presence of metal catalyst to replace halogen or other nucleofugal leaving group [1, 8, 9]. Thus, a two-step synthetic route to ligands **2** employs the Pd-catalyzed Buchwald-Hartwig reaction [10–14] of enantiopure 3-(4,5-dihydro-1,3-oxazol-2-yl)pyridin-2-amines **6** with 3-bromo-5,6-diphenyl-1,2,4-triazine (**7a**) as the key step (Scheme 1). 3-(4,5-Dihydro-1,3-oxazol-2-yl)pyridin-2-amines **6a**–**d** were obtained by condensation of enantiomerically pure aminoalcohols **5a**–**d** with the cyano group of 2-aminopyridine-3-carbonitrile (**4**). This reaction was conducted in the presence of a catalytic amount (20 mol%) of $ZnCl_2$ as Lewis acid [15]. After 4 days of heating in boiling chlorobenzene the appropriate (oxazol-2-yl)pyridin-2-amines **6a**–**d** were isolated with 31–99% yield. Our previously described protocol of condensation of aminoalcohols with 2-aminobenzonitrile requires the use of an excess of $ZnCl_2$, and after removal of solvent, stirring the mixture with NaOH solution to isolate the product [1]. The use of threefold excess of $ZnCl_2$ in the reaction between **4** and **5a**–**d** allowed to shorten the reaction time to 24 h, but isolation of the product from the reaction mixture appeared difficult.



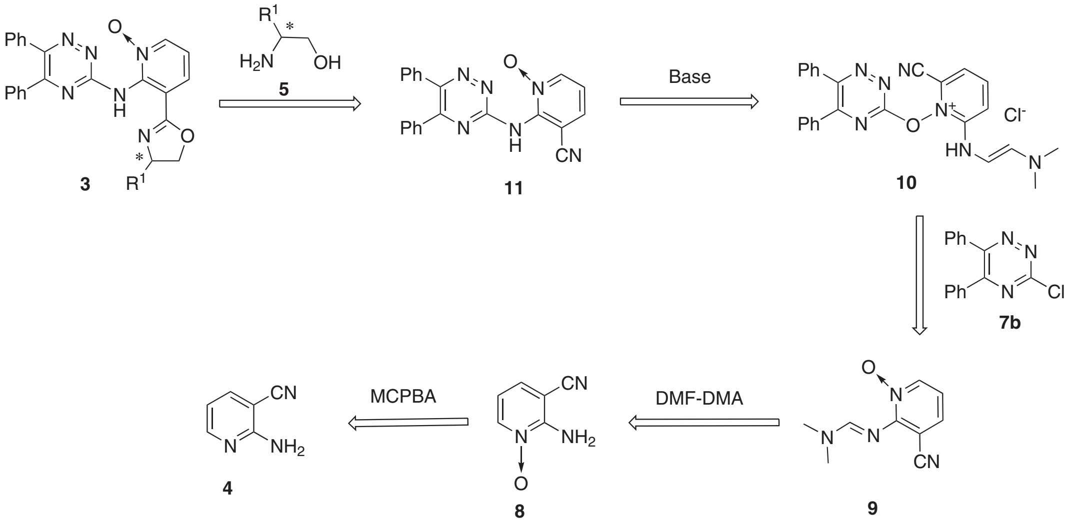
a: $R^1 = t\text{-}Bu\ (S)$
b: $R^1 = Ph\ (S)$
c: $R^1 = i\text{-}Pr\ (S)$
d: $R^1 = Bn\ (R)$

Scheme 1 Synthesis of ligands **2a**–**d**.

After obtaining amines **6**, an attempt to react them with 3-bromo-5,6-diphenyl-1,2,4-triazine (**7a**) was undertaken. To synthesize the ligands **2a**–**d** the application of Buchwald-Hartwig Pd-catalysis was necessary. Thus, the aryl aminations between **7a** and **6a**–**d** were carried out using Pd_2dba_3, Xantphos, and K_2CO_3 in boiling dioxane (Scheme 1). This procedure allowed to obtain the ligands **2a**–**d** in moderate yields ranging from 32% to 37%.

Synthesis of ligands of type **3** could not be accomplished by simple oxidation of **2a**–**d**, since 1,2,4-triazine [16] as well as the oxazoline [17] rings are also susceptible to oxidizing conditions. Initial attempt was made to obtain ligands **3** utilizing amination of 3-halo-1,2,4-triazine with *N*-protected aminopyridine 1-oxides **9** based on aza-Smiles rearrangement (Scheme 2) [18].

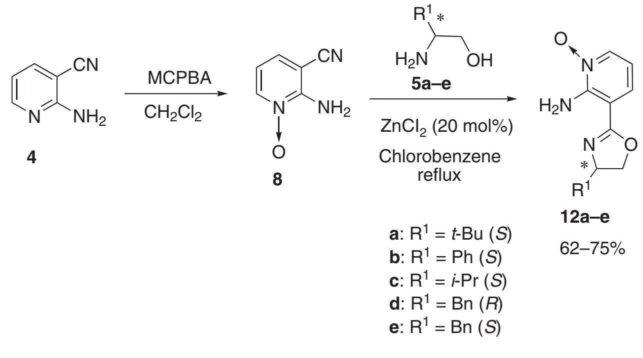
Analogous protocol described by us previously, proved to be effective for amination of pyridine and pyrimidine halides [18, 19]. This approach assumes formation of intermediary salt **10** in reaction of formamidine protected 2-aminopyridine-3-carbonitrile 1-oxide **9** with 3-chloro-5,6-diphenyl-1,2,4-triazine (**7b**). Base-induced rearrangement of **10** should give derivative **11,** the condensation of which with aminoalcohols **5** would produce ligands **3**. A reaction of *N*-oxide **8** with 3 equivalents of *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) was carried out at room temperature without any solvent. After 80 h of stirring, the amidine protected compound **9** was isolated in 92% yield. To our disappointment, the next step, the preparation of salt **10** appeared difficult. A typical procedure for amination of pyridine and pyrimidine halides with



Scheme 2 Proposed synthetic approach to ligands **3**.

formamidine protected aminopyridine 1-oxides involving stirring of the substrates in dry DMF at room temperature in the case of 1,2,4-triazine halide proved to be ineffective. Application of different solvents and changing the reaction temperature did not result in formation of product **10**. Difficulties in formation of salt **10** make the selected synthetic strategy unsuccessful.

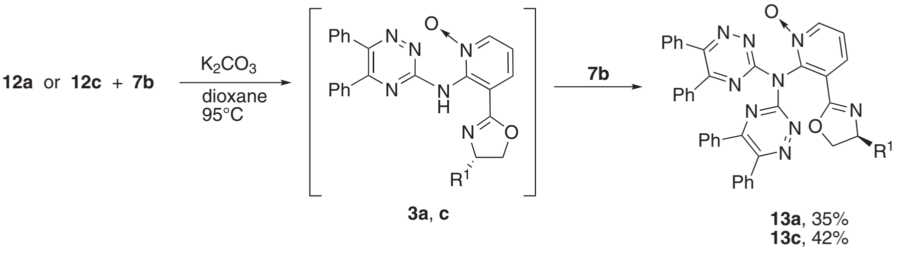
Searching for another method of synthesis of compounds **3** we envisaged a more reliable procedure involving amination of 3-chloro-5,6-diphenyl-1,2,4-triazine (**7b**) with (oxazol-2-yl)pyridin-2-amine 1-oxides **12**. Thus, the synthesis of ligands of type **3** began with preparation of *N*-oxide **8** by oxidizing 2-aminopyridine-3-carbonitrile (**4**) with *m*-chloroperbenzoic acid in dichloromethane (Scheme 3).



Scheme 3 Synthesis of chiral *N*-oxides **12a–e**.

Condensation of *N*-oxide **8** with aminoalcohols **5a–e** yielded the desired 3-(oxazol-2-yl)pyridin-2-amine 1-oxides **12a–e** in good yields. The reaction time was controlled to avoid transformation of the products to oxazolines **6** (see Experimental part). The preparation of ligands **3** was first attempted by heating oxides **12a** and **12c** with 3-chloro-5,6-diphenyl-1,2,4-triazine (**7b**) in dioxane in the presence of K_2CO_3 at 95°C. Under these conditions the unexpected respective products **13a** and **13c** were generated (Scheme 4).

The *N*-oxide function strongly activates the amino group in compounds **12**, so the substitution of the chlorine atom in **7b** can proceed under metal-free conditions. Moreover, the secondary NH group in **3a** and **3c** is also active enough to react with a second molecule of 3-chlorotriazine **7b** to give compounds **13a** and **13c**. To inhibit the reaction of the initially formed compounds **3a** and **3c**



Scheme 4 Reaction of *N*-oxides **12a** and **12c** with 3-chloro-5,6-diphenyl-1,2,4-triazine (**7b**).

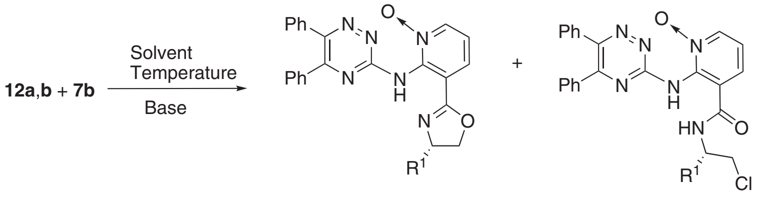
with 3-chlorotriazine, K_2CO_3 was eliminated from the reaction mixture. Under base-free conditions at 95°C product **3a** was obtained in 22% yield accompanied by undesired compound **14a** isolated in the yield of 54% (Table 1, entry 1). When the temperature was lowered to 20°C, no reaction between **12a** and **7b** occurred (Table 1, entry 2). In DMF at 50°C the expected product **3a** and unexpected compound **14a** were formed in 15% and 48% yield, respectively (Table 1, entry 3). Under these conditions, *N*-oxide **12b** reacted with chlorotriazine **7b** giving compounds **3b** and **14b** in 10% and 48% respective yields after chromatography (Table 1, entry 4). Chemically pure compounds **3a**,**b** and **14a**,**b** were characterized by several analytical techniques including ^{1}H NMR, ^{13}C NMR, IR, HR MS, which confirmed their structures.

Undesirable compounds **14a**,**b** were formed by transformation of initially formed products **3a**,**b**. Since the reaction of (oxazol-2-yl)pyridin-2-amine 1-oxides **12** with 3-chloro-5,6-diphenyl-1,2,4-triazine (**7b**) is conducted in the absence of base, evolving hydrochloride protonates the nitrogen atom of the oxazoline ring in **3a**,**b** activating these compounds towards nucleophilic attack of chloride ion. This leads to opening of the oxazoline ring giving rise to products **14a**,**b** (Scheme 5).

The observed reactivity was confirmed in the reactions of three other (oxazol-2-yl)pyridin-2-amine 1-oxides **12c**–**e** with 3-chloro-5,6-diphenyl-1,2,4-triazine (**7b**). In each case the formation of two products **3c**–**e** and **14c**–**e** was observed. Attempts to separate the products **3c**–**e** and **14c**–**e** by chromatography failed. They were not isolated in chemically pure form. Formation of **3c**–**e** and **14c**–**e** was shown on the basis of analysis of mass spectra of their mixtures. The ESI HR mass spectrum of a mixture of **3c** and **14c** shows signals at *m/z* 453.2039 and *m/z* 489.1804 corresponding to the values expected for [**3c**+H]$^+$ and [**14c**+H]$^+$. The mass spectrum of the mixture of **3d** and **14d** indicates the presence of ions of *m/z* 501.2039 and *m/z* 537.1780 which match the calculated masses of [**3d**+H]$^+$ and [**14d**+H]$^+$. Analogously, ions with *m/z* 501.2036 and *m/z* 537.1798 are observed for the mixture of **3e** and **14e**. Their masses are virtually identical with the masses calculated for [**3e**+H]$^+$ and [**14e**+H]$^+$.

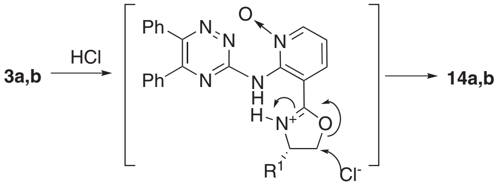
The cationic activated oxazoline ring-opening process under an attack of nucleophile gained synthetic importance, for example in the synthesis of polymers [20, 21]. To circumvent the problem with conversion of **3** to **14**, the use of organic bases in the reaction of **12** with **7b** was considered. It was predicted that aliphatic amines such as triethylamine or DABCO can form salts with 3-chlorotriazine **7b**, as observed previously [22] and their use was excluded. Therefore, the reaction of **12b** and **7b** was repeated with 2 equivalents of *N*,*N*-dimethylaniline, *m*-nitroaniline or *p*-nitroaniline. Unfortunately, no significant improvement in yield of the desired product **3b** was achieved. Compound **3b** isolated in yield 17–24% was still accompanied by its transformation product **14b** (45–52%, Table 1, entry 6, 7, and 8). As can be seen from the results summarized in Table 1, in the reaction of **12b** and **7b** approximately 70% of the substrates are initially converted to the desired product **3b** but about 50% of the product is transformed to the open-chain compound **14b**.

Table 1 Reactions of *N*-oxides **12a,b** with 3-chloro-5,6-diphenyl-1,2,4-triazine (**7b**).



3a,**b** **14a**,**b**

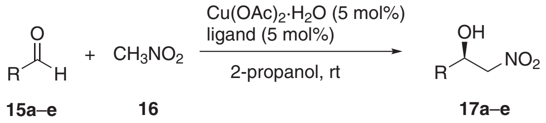
	R¹	Substrate	Solvent	Base	Temperature °C	Yield%	
						3	14
1	*t*-Bu	**12a**	Dioxane	–	95	22	54
2	*t*-Bu	**12a**	Dioxane	–	20	–	–
3	*t*-Bu	**12a**	DMF	–	50	15	48
4	Ph	**12b**	DMF	–	50	10	48
6	Ph	**12b**	DMF	*N*,*N*-dimethylaniline	50	19	51
7	Ph	**12b**	DMF	*m*-Nitroaniline	50	24	45
8	Ph	**12b**	DMF	*p*-Nitroaniline	50	17	52



Scheme 5 Formation of compounds **14a,b**.

Initial study was focused on the screening of ligands **2** and **3** in the copper catalyzed enatioselective nitroaldol reaction. Several aldehydes were treated with nitromethane in the presence of *in situ* generated complexes of ligands **2** and **3** with $Cu(OAc)_2{\cdot}H_2O$. The reactions were carried out in 2-propanol at room temperature and lead to β-nitro alcohols with moderate to good chemical yield but no enantioselectivity was observed (Table 2). Enantiopure compounds **13c** and **14b** were also screened in the attempted enantioselective addition of nitromethane to *m*-nitrobenzaldehyde. The β-nitro alcohols formed in the respective yields of 42% and 56% and were isolated as mixtures of enantiomers, which indicates that the compounds **13c** and **14b** are also not good enantiomeric catalysts in the nitroaldol reaction (Table 2).

Table 2 Screening of ligands **2**, **3**, **13c**, and **14b** in the catalytic enantioselective Henry reaction.[a]



	R	Aldehyde	Ligand	Product	Yield[b] %	ee[c] %
1	$3\text{-}NO_2C_6H_4$	**15a**	**2a**	**17a**	67	7 (*S*)
2	$3\text{-}NO_2C_6H_4$	**15a**	**2c**	**17a**	75	4 (*S*)
3	$3\text{-}NO_2C_6H_4$	**15a**	**2d**	**17a**	79	rac
4	$3\text{-}NO_2C_6H_4$	**15a**	**3b**	**17a**	79	rac
5	$4\text{-}NO_2C_6H_4$	**15b**	**3b**	**17b**	65	rac
6	$2\text{-}ClC_6H_4$	**15c**	**3b**	**17b**	83	rac
7	$2\text{-}BrC_6H_4$	**15c**	**3b**	**17c**	77	rac
8	$3\text{-}MeC_6H_4$	**15d**	**3b**	**17d**	29	rac
9	$2\text{-}MeOC_6H_4$	**15e**	**3b**	**17e**	49	rac
10	$3\text{-}NO_2C_6H_4$	**15a**	**13c**	**17a**	42	rac
11	$3\text{-}NO_2C_6H_4$	**15a**	**14b**	**17a**	56	rac

[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 checked by HPLC using Chiracel OD-H column.

Conclusion

A new class of chiral compounds **2** with three different heterocyclic rings in their structure have been prepared by employing Pd-catalyzed Buchwald-Hartwig cross-coupling reaction between the enantiopure 3-(4,5-dihydro-1,3-oxazol-2-yl)pyridin-2-amines **6** and 3-bromo-5,6-diphenyl-1,2,4-triazine (**7a**) as the key step. Two different synthetic routes towards compounds **3** containing *N*-oxide functionality were investigated: amination of 3-chloro-5,6-diphenyl-1,2,4-triazine with *N*-protected aminopyridine 1-oxide **9** based on aza-Smiles rearrangementand and amination of 3-chloro-1,2,4-triazine with enantiopure 3-[4-R/Ar-4,5-dihydro-1,3-oxazol-2-yl] pyridine-2-amine 1-oxides **12**. The use of the former compound failed due to difficulties in formation of salt **10**. The second method encountered problems with unexpected subsequent reactions of initially formed product **3**. Under basic conditions, product **3** acts as good nucleophile and undergoes reaction with a second molecule of **7b** giving compounds **13**. In the experiments carried out in the absence of a base or in the presence of a weak organic base, initially formed product **3** undergoes the oxazoline ring opening leading to compound **14**. These new classes of oxazoline ligands **2** and **3** do not exhibit enantio-controlling abilities in the copper catalyzed enantioselective Henry reaction. This result may indicate a different mode of copper complexation with ligands **2** and **3** in comparison to ligands **1**. The nitrogen atom of the pyridine ring or the oxygen atom of the *N*-oxide function can be involved in complexation with the copper ion. The stereogenic center of the complex may be located at some distance of the Lewis acid center and does not have any influence on the stereochemical course of the nitroaldol reaction. This issue needs further explanation and will be discussed in due course.

Experimental

^1H and ^{13}C NMR spectra were determined at 400 MHz and 100 MHz, respectively, on a Varian 400 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 analyzes were obtained with a Elementar Vario EL III CHNS analyzer. Optical rotation values were measured at room temperature with a Perkin-Elmer polarimeter. The *ee* values were checked by HPLC (Knauer) analysis by using a chiral stationary phase column (Chiralcel OD-H), and eluting with 2-propanol–hexanes. Thin layer chromatography (TLC) was carried out on aluminium sheets coated 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 [23] and 3-bromo-5,6-diphenyl-1,2,4-triazine [1] were synthesized according to literature procedures.

Synthesis of 2-aminopyridine-3-carbonitrile 1-oxide (8)

A solution of 2-aminopyridine-3-carbonitrile (**4**, 950 mg, 8 mmol) in dichloromethane (30 mL) was cooled to -10°C and treated dropwise with a solution of *m*-chloroperbenzoic acid (1656 mg, 9.6 mmol) in dichloromethane (15 mL). The resulting mixture was stirred at -10°C for 3 h and then at room temperature for 20 h. The product was filtered off, washed with ethyl ether and dried undera reduced pressure; yield 88% (950 mg); mp 238–239°C; IR (ZnSe): 3271, 3099, 3076, 3057, 2225, 1620, 1581, 1506, 1446, 1215 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.35 (dd, 1H, *J* = 1.2 Hz, *J* = 6.4 Hz), 7.73 (br s, 2H), 7.57 (dd, 1H, *J* = 1.2 Hz, *J* = 8.0 Hz), 6.69 (dd, 1H, *J* = 6.4 Hz, *J* = 8.0 Hz); ^{13}C NMR (DMSO-d_6): δ 152.3, 140.8, 130.9, 115.2, 112.1, 91.3. Anal. Calcd for $C_6H_5N_3O$ (135.12): C, 53.33; H, 3.73; N, 31.10. Found: C, 53.37; H, 3.76; N, 31.16.

Synthesis of 3-cyano-2-[(dimethylamino)methyleneamino]-pyridine 1-oxide (9)

2-Aminopyridine-3-carbonitrile 1-oxide (**8**, 135 mg, 1 mmol) was treated with DMF-DMA (0.4 mL, 3 mmol). The mixture was placed in the ultrasonic bath for 15 min and then stirred at room temperature for 80 h. Next, the suspension was dissolved in CCl_4 and the solvent was evaporated. The dissolving-evaporating procedure was repeated five times to obtain analytically pure product **9**; yield 92% (175 mg); mp 110–112°C; IR (ZnSe): 2227, 1608, 1570, 1517, 1199, 1109 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 10.03 (s, 1H), 8.17 (dd, 1H, *J* = 1.6 Hz, *J* = 6.8 Hz), 7.41 (dd, 1H, *J* = 1.6 Hz, *J* = 7.8 Hz), 6.70 (dd, 1H, *J* = 6.8 Hz, *J* = 7.8 Hz), 3.17 (s, 3H), 3.15 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 156.9, 152.3, 143.1, 131.1, 116.0, 115.1, 106.6, 40.9, 33.9. HRMS (ESI). Calcd for $C_9H_{11}N_4O$ ([M+H]$^+$): *m/z* 191.0927. Found: *m/z* 191.0928.

General procedure for the synthesis of 3-(4,5-dihydro-1,3-oxazol-2-yl)pyridin-2-amines 6a–d and *N*-oxides 12a–e

An oven dried two-necked flask was filled with argon and charged with 2-aminopyridine-3-carbonitrile (**4**, 119 mg, 1 mmol) or 2-aminopyridine-3-carbonitrile 1-oxide (**8**, 135 mg, 1 mmol), the appropriate amino alcohol (1.5 mmol), and anhydrous chlorobenzene (6 mL). The mixture was heated to 60°C and freshly flame-dried $ZnCl_2$ (27 mg, 20 mol%) was added. The mixture was stirred under reflux for the indicated period of time. The solvent was then removed under reduced pressure and the product was extracted with dichloromethane and purified as described below.

3-[(4*S*)-4-*tert*-Butyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine-2-amine (6a) Compound was prepared from (*S*)-2-amino-3,3-dimethylbutan-1-ol (176 mg, 1.5 mmol) and 2-aminopyridine-3-carbonitrile after 4 days of heating. The product was isolated by silica gel chromatography (hexane/EtOAc, 5:1) and crystallized from hexanes; yield 69% (151 mg); mp 69°C; $[\alpha]_D^{20}$ = +13.9 (*c* 0.98, CH_2Cl_2); IR (ZnSe): 3336, 3155, 2953, 1639, 1616, 1467, 1456, 1261, 773 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.12 (dd, 1H, *J* = 1.8 Hz, *J* = 5.2 Hz), 7.90 (dd, 1H, *J* = 1.8 Hz, *J* = 7.8 Hz), 6.60 (dd, 1H, *J* = 5.2 Hz, *J* = 7.8 Hz), 4.29–4.22 (m, 1H), 4.16–4.07 (m, 1H), 2.95 (br s, 2H), 0.93 (s, 9H); ^{13}C NMR ($CDCl_3$) δ: 162.2, 158.2, 151.0, 137.8, 122.2, 104.7, 67.5, 33.8, 25.8. Anal. Calcd for $C_{12}H_{17}N_3O$ (219.28): C, 65.73; H, 7.81; N, 19.16. Found: C, 65.77; H, 7.75; N, 19.07.

3-[(4*S*)-4-Phenyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine-2-amine (6b) Compound was prepared from (*S*)-2-phenylglycinol (105 mg, 1.5 mmol) and 2-aminopyridine-3-carbonitrile after 4 days of heating. The product was isolated by silica gel chromatography (hexane/EtOAc, 3:1) and recrystallized from hexanes; yield 99% (236 mg); mp 70–71°C; $[\alpha]_D^{20}$ = +159.5 (*c* 1.05, CH_2Cl_2); IR (ZnSe): 3330, 3152, 2950, 1638, 1614, 1464, 1453, 1260, 771 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.18 (dd, 1H, *J* = 1.9 Hz, *J* = 4.8 Hz), 7.99 (dd, 1H, *J* = 1.9 Hz, *J* = 7.6 Hz), 7.39–7.35 (m, 2H), 7.32–7.28 (m, 3H), 6.65 (dd, 1H, *J* = 4.8 Hz, *J* = 7.6 Hz), 5.45 (dd, 1H, *J* = 8.3 Hz, *J* = 10.0 Hz), 4.73 (dd, 1H, *J* = 8.3 Hz, *J* = 10.0 Hz), 4.17 (t, 1H, *J* = 8.3 Hz), amino group protons were exchanged with deuterium; ^{13}C NMR ($CDCl_3$): δ 163.8, 158.3, 151.5, 142.2, 138.2, 128.8, 127.7, 126.5, 112.3, 104.4, 73.7, 70.1. HRMS (ESI). Calcd for $C_{14}H_{14}N_3O$ ([M+H]$^+$): *m/z* 240.1131. Found: *m/z* 240.1131.

3-[(4*S*)-4-Isopropyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine-2-amine (6c) Compound was prepared from (*S*)-valinol (155 mg, 1.5 mmol) and 2-aminopyridine-3-carbonitrile after 4 days of heating. The product was isolated by silica gel chromatography (hexane/EtOAc, 3:1) and crystallized from hexanes; yield 31% (64 mg); mp 100–101°C; $[\alpha]_D^{20}$ = -8.5 (*c* 1.03, CH_2Cl_2); IR (KBr): 3309, 3136, 2954, 2364, 1638, 1577, 1450, 1363, 1258, 1068, 1037 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.11 (dd, 1H, *J* = 1.9 Hz, *J* = 4.9 Hz), 7.90 (dd, 1H, *J* = 1.9 Hz, *J* = 7.7 Hz), 6.59 (dd, 1H, *J* = 4.9 Hz, *J* = 7.7 Hz), 4.34 (dd, 1H, *J* = 7.9 Hz, *J* = 9.2 Hz), 4.12–4.06 (m, 1H), 4.02 (t, 1H, *J* = 7.9 Hz), 1.89 (br s, 2H), 1.81–1.73 (m, 1H), 1.01 (d, 3H, *J* = 6.7 Hz), 0.93 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$): δ 162.3, 158.2, 137.8, 112.2, 104.7, 72.9, 69.4, 33.1, 18.9, 18.6. Anal. Calcd for $C_{11}H_{15}N_3O$ (205.26): C, 64.37; H, 7.37; N, 20.47. Found: C, 64.39; H, 7.31; N, 20.36.

3-[(4*R*)-4-Benzyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine-2-amine (6d) Compound was prepared from (*R*)-2-amino-3-phenylpropan-1-ol (227 mg, 1.5 mmol) and 2-aminopyridine-3-carbonitrile after 4 days. The product was purified by silica gel chromatography (CH_2Cl_2/MeOH, 40:1); yield 74% (187 mg), yellow oil; $[\alpha]_D^{20}$ = -23.9 (*c* 1.39, CH_2Cl_2); IR (KBr): 3334, 3158, 2949, 1632, 1615, 1459, 1450, 1265, 778 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.14 (dd, 1H, *J* = 1.8 Hz, *J* = 4.8 Hz), 7.90 (dd, 1H, *J* = 1.8 Hz, *J* = 7.6 Hz), 7.34–7.30 (m, 2H), 7.25–7.21 (m, 3H), 6.60 (dd, 1H, *J* = 4.8 Hz, *J* = 7.6 Hz), 4.66–4.60 (m, 1H), 4.32 (dd, 1H, *J* = 8.0 Hz, *J* = 8.8 Hz), 4.06 (dd, 1H, *J* = 8.0 Hz, *J* = 8.8 Hz), 3.11 (dd, 1H, *J* = 7.0 Hz, *J* = 13.6 Hz), 2.78 (dd, 1H, *J* = 7.0 Hz, *J* = 13.6 Hz), amino group protons were exchanged with deuterium; ^{13}C NMR ($CDCl_3$): δ 162.8, 158.2, 151.3, 138.0, 137.9, 129.2, 128.5, 126.5, 112.3, 104.6, 70.8, 68.0, 42.1. HRMS (ESI). Calcd for $C_{15}H_{16}N_3O$ ([M+H]$^+$): *m/z* 254.1288. Found: *m/z* 254.1287.

3-[(4*S*)-4-*tert*-Butyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine-2-amine 1-oxide (12a) Compound was prepared from (*S*)-2-amino-3,3-dimethylbutan-1-ol (176 mg, 1.5 mmol) and

2-aminopyridine-3-carbonitrile 1-oxide after 60 h of heating. The product was isolated by silica gel chromatography (CH_2Cl_2/MeOH, 10:1) and crystallized from hexanes; yield 75% (176 mg); mp 128–129°C; $[\alpha]_D^{20}$ = +41.8 (*c* 1.02, CH_2Cl_2); IR (KBr): 3320, 3220, 2952, 2870, 1620, 1611, 1446, 1210 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.86 (br s, 2H), 8.20 (dd, 1H, *J* = 1.6 Hz, *J* = 6.4 Hz), 7.62 (dd, 1H, *J* = 1.2 Hz, *J* = 8.0 Hz), 6.57 (dd, 1H, *J* = 6.4 Hz, *J* = 7.6 Hz), 4.32 (dd, 1H, *J* = 8.4 Hz, *J* = 9.6 Hz), 4.21–4.11 (m, 2H), 0.94 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 161.0, 150.8, 139.0, 128.4, 110.2, 106.9, 76.3, 68.1, 33.8, 25.8. Anal. Calcd for $C_{12}H_{17}N_3O_2$ (235.28): C, 61.26; H, 7.28; N, 17.86. Found: C, 61.28; H, 7.11; N, 17.83.

3-[(4*S*)-4-Phenyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine-2-amine 1-oxide (12b) Compound was prepared from (*S*)-2-phenylglicinol (105 mg, 1.5 mmol) and 2-aminopyridine-3-carbonitrile 1-oxide after 24 h of heating. The product was isolated by silica gel chromatography (CH_2Cl_2/MeOH, 30:1) and recrystallized from the mixture of hexanes and EtOAc; yield 73% (186 mg); mp 108–109°C; $[\alpha]_D^{20}$ = +257.5 (*c* 1.04, CH_2Cl_2); IR (KBr): 3250, 1620, 1540, 1446, 1220 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.76 (br s, 2H), 8.23 (dd, 1H, *J* = 1.2 Hz, *J* = 6.4 Hz), 7.70 (dd, 1H, *J* = 1.2 Hz, *J* = 8.0 Hz), 7.40–7.27 (m, 5H), 6.61 (dd, 1H, *J* = 6.4 Hz, *J* = 8.0 Hz), 5.49 (dd, 1H, *J* = 8.4 Hz, *J* = 10.0 Hz), 4.78 (dd, 1H, *J* = 8.4 Hz, *J* = 10.0 Hz), 4.22 (t, 1H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$): δ 162.6, 150.9, 141.6, 139.1, 128.9, 128.0, 127.9, 126.5, 110.4, 106.4, 74.1, 70.2. Anal. Calcd for $C_{14}H_{13}N_3O_2$ (255.27): C, 65.87; H, 5.13; N, 16.46. Found: C, 65.93; H, 5.12; N, 16.36.

3-[(4*S*)-4-Isopropyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine-2-amine 1-oxide (12c) Compound was prepared from (*S*)-valinol (155 mg, 1.5 mmol) and 2-aminopyridine-3-carbonitrile 1-oxide after 40 h of heating. The product was isolated by silica gel chromatography (CH_2Cl_2/MeOH, 30:1) and crystallized from hexanes; yield 62% (137 mg); mp 130–131°C; $[\alpha]_D^{20}$ = +22.0 (*c* 1.01, CH_2Cl_2); IR (KBr): 3346, 3228, 2958, 2873, 1643, 1614, 1548, 1446, 1192 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.80 (br s, 2H), 8.18 (dd, 1H, *J* = 1.6 Hz, *J* = 6.4 Hz), 7.60 (dd, 1H, *J* = 1.6 Hz, *J* = 8.0 Hz), 6.56 (dd, 1H, *J* = 6.8 Hz, *J* = 8.0 Hz), 4.39 (dd, 1H, *J* = 7.6 Hz, *J* = 9.2 Hz), 4.18–4.06 (m, 2H), 1.87–1.77 (m, 1H), 1.02 (d, 3H, *J* = 6.8 Hz), 0.94 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 161.1, 150.7, 138.9, 127.7, 110.3, 106.8, 72.9, 69.9, 33.0, 18.8, 18.5. Anal. Calcd for $C_{11}H_{15}N_3O_2$ (221.25): C, 59.71; H, 6.83; N, 18.99. Found: C, 59.82; H, 6.87; N, 18.93.

3-[(4*R*)-4-Benzyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine-2-amine 1-oxide (12d) Compound was prepared from (*R*)-2-amino-3-phenylpropan-1-ol (227 mg, 1.5 mmol) and 2-aminopyridine-3-carbonitrile 1-oxide after 42 h of heating. The product was isolated by silica gel chromatography (CH_2Cl_2/MeOH, 20:1) and crystallized from a mixture of hexanes and EtOAc; yield 73% (196 mg); mp 134–135°C; $[\alpha]_D^{20}$ = -77.5 (*c* 1.02, CH_2Cl_2); IR (KBr): 3379, 3250, 3040, 2884, 1642, 1614, 1546, 1455, 1194 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.75 (br s, 2H), 8.20 (dd, 1H, *J* = 1.2 Hz, *J* = 6.4 Hz), 7.58 (dd, 1H, *J* = 1.2 Hz, *J* = 8.0 Hz), 7.33–7.22 (m, 5H), 6.56 (dd, 1H, *J* = 6.4 Hz, *J* = 8.0 Hz), 4.67–4.62 (m, 1H), 4.37 (t, 1H, *J* = 8.4 Hz), 4.11 (dd, 1H, *J* = 7.6 Hz, *J* = 8.4 Hz), 3.10 (dd, 1H, *J* = 6.4 Hz, *J* = 13.6 Hz), 2.83 (dd, 1H, *J* = 7.6 Hz, *J* = 14.0 Hz); ^{13}C NMR ($CDCl_3$): δ 161.7, 150.7, 139.0, 137.5, 129.2, 128.6, 127.8, 126.7, 110.3, 106.6, 71.3, 68.0, 41.8. Anal. Calcd for $C_{15}H_{15}N_3O_2$ (269.30): C, 66.90; H, 5.61; N, 15.60. Found: C, 66.91; H, 5.64; N, 15.52.

3-[(4*S*)-4-Benzyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine-2-amine 1-oxide (12e) Compound was prepared from (*S*)-2-amino-3-phenylpropan-1-ol (227 mg, 1.5 mmol) and 2-aminopyridine-3-carbonitrile 1-oxide after 47 h of heating. The product was isolated by silica gel chromatography (CH_2Cl_2/MeOH, 30:1) and crystallized from a mixture of hexanes and EtOAc; yield 72% (194 mg); mp 134–136°C; $[\alpha]_D^{20}$ = +76.8 (*c* 0.52, CH_2Cl_2); IR (KBr): 3385, 3251, 3034, 2893, 1641, 1548, 1454, 1193 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.72 (br s, 2H), 8.15 (d, 1H, *J* = 6.9 Hz), 7.53 (d, 1H, *J* = 6.9 Hz), 7.28–7.17 (m, 5H), 6.51 (t, 1H, *J* = 6.9 Hz), 4.63–4.56 (m, 1H), 4.31 (t, 1H, *J* = 9.2 Hz), 4.06 (t, 1H, *J* = 8.0 Hz), 3.04 (dd, 1H, *J* = 6.8 Hz, *J* = 13.6 Hz), 2.77 (dd, 1H, *J* = 6.8 Hz, *J* = 13.6 Hz); ^{13}C NMR ($CDCl_3$): δ 161.4, 150.4, 138.8, 137.3, 129.0, 128.4, 127.9, 126.4, 110.2, 106.5, 71.0, 67.7, 41.6. HRMS (ESI). Calcd for $C_{15}H_{16}N_3O_2$ ($[M+H]^+$): *m/z* 270.1237. Found: *m/z* 270.1236.

General procedure for the preparation of ligands 2a–d

An oven-dried three-necked flask was filled with argon and charged with Pd_2dba_3 (45.8 mg, 10 mol%), Xantphos (57.8 mg, 20 mol%), 3-(oxazol-2-yl)pyridine-2-amine **6a–d** (0.6 mmol), 3-bromo-5,6-diphenyl-1,2,4-triazine (**7a**, 156 mg, 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 a septum and the mixture was heated under reflux for the indicated period of time. After cooling, the solid material was filtered off and washed with CH_2Cl_2. The solvent was evaporated, and the resulting crude product was purified as described below.

5,6-Diphenyl-3-{3-[(4*S*)-4-*tert*-butyl- 4,5-dihydro-1,3-oxazol-2-yl]pyridin-2-yl}amino-1,2,4-triazine (2a) The product was obtained from 3-[(4*S*)-4-*tert*-butyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine-2-amine (**6a**) after 24 h of heating as a yellow solid, purified by column chromatography (CH_2Cl_2/MeOH, 30:1) and crystallized from ethanol; yield 36% (81 mg); mp 204–206°C; $[\alpha]_D^{20}$ = –1.7 (*c* 0.54, CH_2Cl_2); IR (ZnSe): 3057, 2958, 1631, 1610, 1506, 1435, 1390, 1053, 759, 696 cm^{-1}; ^1H NMR ($CDCl_3$): δ 12.74 (s, 1H), 8.60 (dd, 1H, *J* = 1.6 Hz, *J* = 4.8 Hz), 8.13 (dd, 1H, *J* = 2.0 Hz, *J* = 7.6 Hz), 7.65–7.63 (m, 2H), 7.58–7.54 (m, 2H), 7.40–7.29 (m, 6H), 6.99 (dd, 1H, *J* = 5.2 Hz, *J* = 8.0 Hz), 4.41–4.36 (m, 1H), 4.27–4.22 (m, 2H), 1.03 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 161.9, 158.0, 155.8, 152.3, 151.9, 151.0, 137.7, 136.0, 135.9, 130.5, 129.9, 129.3, 128.7, 128.4, 128.3, 116.4, 108.6, 76.2, 68.1, 34.0, 25.9. Anal. Calcd for $C_{27}H_{26}N_6O$ (450.53): C, 71.98; H, 5.82; N, 18.65. Found: C, 71.81; H, 5.79; N, 18.61.

5,6-Diphenyl-3-{3-[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]pyridin-2-yl}amino-1,2,4-triazine (2b) The product was obtained from 3-[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine-2-amine (**6b**) after 22 h of heating as a yellow solid, purified by column chromatography (CH_2Cl_2/MeOH, 30:1) and crystallized from ethanol; yield 32% (75 mg); mp 104–105°C; $[\alpha]_D^{20}$ = +212.9 (*c* 0.51, CH_2Cl_2); IR (ZnSe): 3026, 2887, 1614, 1504, 1442, 1413, 1350, 1128, 1041, 958, 763, 694 cm^{-1}; ^1H NMR ($CDCl_3$): δ 12.38 (s, 1H), 8.62 (dd, 1H, *J* = 1.8 Hz, *J* = 4.8 Hz), 8.22 (dd, 1H, *J* = 1.8 Hz, *J* = 7.8 Hz), 7.62–7.60 (m, 2H), 7.56–7.41 (m, 2H), 7.40–7.29 (m, 11H), 7.04 (dd, 1H, *J* = 4.8 Hz, *J* = 7.8 Hz), 5.61 (dd, 1H, *J* = 8.4 Hz, *J* = 10.0 Hz), 4.84 (dd, 1H, *J* = 8.4 Hz, *J* = 10.0 Hz), 4.29 (t, 1H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$): δ 163.2, 158.0, 155.9, 152.4, 152.1, 151.3, 141.6, 138.1, 135.9, 130.4, 130.0, 129.3, 128.8, 128.7, 128.4, 128.3, 127.7, 126.4, 116.6, 108.5, 73.9, 69.9. HRMS (ESI). Calcd for $C_{29}H_{23}N_6O$ ($[M+H]^+$): *m/z* 471.1928. Found: *m/z* 471.1921.

5,6-Diphenyl-3-{3-[(4*S*)-4-isopropyl- 4,5-dihydro-1,3-oxazol-2-yl)pyridin-2-yl]amino-1,2,4-triazine (2c) The product was obtained from 3-[(4*S*)-4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine-2-amine (**6c**) after 21 h of heating as a yellow solid, purified by column chromatography (CH_2Cl_2/MeOH, 30:1) and crystallized from ethanol; yield 35% (76 mg); mp 158–160°C; $[\alpha]_D^{20}$ = +1.5 (*c* 0.52, CH_2Cl_2); IR (ZnSe): 2.960, 2926, 2899, 2881, 1643, 1627, 1516, 1442, 1396, 1049, 765, 694 cm^{-1}; ^1H NMR ($CDCl_3$): δ 12.65 (s, 1H), 8.59 (dd, 1H, *J* = 1.9 Hz, *J* = 4.8 Hz), 8.13 (dd, 1H, *J* = 1.9 Hz, *J* = 7.7 Hz), 7.62–7.64 (m, 2H), 7.54–7.56 (m, 2H), 7.40–7.29 (m, 6H), 7.00 (dd, 1H, *J* = 4.8 Hz, *J* = 7.7 Hz), 4.46 (dd, 1H, *J* = 8.2 Hz, *J* = 9.3 Hz), 4.26–4.20 (m, 1H), 4.13 (t, 1H, *J* = 8.1 Hz), 1.90–1.82 (m, 1H), 1.14 (d, 3H, *J* = 6.7 Hz), 1.01 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$): δ 162.7, 158.8, 156.6, 153.0, 152.7, 151.7, 138.4, 136.7, 136.6, 131.1, 130.6, 129.9, 129.4, 129.0, 128.9, 117.0, 109.2, 73.2, 70.5, 33.5, 19.0, 18.9. Anal. Calcd for $C_{26}H_{24}N_6O$ (436.51): C, 71.54; H, 5.54; N, 19.25. Found: C, 71.51; H, 5.61; N, 19.18.

5,6-Diphenyl-3-{3-[(4*R*)-4-benzyl-4,5-dihydro-1,3-oxazol-2-yl]pyridin-2-yl}amino-1,2,4-triazine (2d) The product was obtained from 3-[(4*R*)-4-benzyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine-2-amine (**6d**) after 18 h of heating as a yellow solid, purified by column chromatography (CH_2Cl_2/MeOH, 30:1) and crystallized from ethanol; yield 37% (89 mg); mp 168–170°C; $[\alpha]_D^{20}$ = -24.6 (*c* 0.53, CH_2Cl_2); IR (ZnSe): 3061, 2887, 1643, 1604, 1496, 1440, 1411, 1346, 1047, 767, 694 cm^{-1}; ^1H NMR ($CDCl_3$): δ 12.38 (s, 1H), 8.58 (dd, 1H, *J* = 1.8 Hz, *J* = 5.0 Hz), 8.12 (dd, 1H, *J* = 1.8 Hz, *J* = 7.8 Hz), 7.63–7.58 (m, 2H), 7.57–7.56 (m, 2H), 7.44–7.24 (m, 9H), 7.21–7.17 (m, 2H), 7.00 (dd, 1H, *J* = 5.0 Hz, *J* = 7.6 Hz), 4.79–4.71 (m, 1H), 4.41 (t, 1H, *J* = 8.2 Hz), 4.16 (t, 1H, *J* = 8.2 Hz), 3.25 (dd, 1H, *J* = 6.8 Hz, *J* = 14.0 Hz), 2.87 (dd, 1H, *J* = 6.8 Hz, *J* = 14.0 Hz); ^{13}C NMR ($CDCl_3$): δ 162.4, 158.0, 156.0, 152.3, 152.1, 151.1, 137.9, 137.5, 136.0, 135.9, 130.4, 130.0, 129.3, 128.8, 128.6, 128.4, 128.3, 126.6, 116.6, 108.6, 71.1, 67.9, 41.7. HRMS (ESI). Calcd for $C_{30}H_{25}N_6O$ ($[M+H]^+$): *m/z* 485.2084. Found: *m/z* 485.2088.

Procedure for the reaction of 3-chloro-5,6-diphenyl-1,2,4-triazine (7b) with (4,5-dihydro-1,3-oxazol-2-yl) pyridine-2-amine 1-oxides in the presence of K_2CO_3

A mixture of 3-chloro-5,6-diphenyl-1,2,4-triazine (**7b**, 267 mg, 1 mmol), appropriate [4,5-dihydro-1,3-oxazol-2-yl]pyridine-2-amine 1-oxide (1.1 mmol), and K_2CO_3 (415 mg, 3 mmol) were placed in round-bottom flask. Then, freshly dried dioxane (16 mL) was added and the mixture was heated at 95°C 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 as described below.

2-[Bis(5,6-diphenyl-1,2,4-triazin-3-yl)amino]-3-[(4*S*)-4-*tert*-butyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine 1-oxide (13a) Compound was prepared from 3-[(4*S*)-4-*tert*-butyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine-2-amine 1-oxide (**12a**, 259 mg, 1.1 mmol), purified by silica gel chromatography (dichloromethane/methanol, 30:1) and crystallized from hexanes/EtOAc; yield 35% (61 mg); mp 134–136°C; $[\alpha]_D^{20}$ = -17.0 (*c* 0.61, CH_2Cl_2); IR (KBr): 3059, 2956, 2868, 1651, 1517, 1490, 1398, 1365, 1280, 1062, 769, 696 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.43 (dd, 1H, *J* = 1.6 Hz, *J* = 6.8 Hz), 7.95 (dd, 1H, *J* = 1.6 Hz, *J* = 4.8 Hz), 7.54–7.47 (m, 9H), 7.41–7.32 (m, 10H), 7.24–7.19 (m, 2H), 4.15 (dd, 1H, *J* = 8.6 Hz, *J* = 10.0 Hz), 3.98 (t, 1H, *J* = 8.6 Hz), 3.85 (dd, 1H, *J* = 8.6 Hz, *J* = 10.0 Hz), 0.61 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 159.0, 158.9, 158.1, 156.7, 156.6, 153.9, 145.8, 141.1, 135.7, 135.6, 135.5, 135.4, 130.5, 130.4, 130.1, 130.0, 129.4, 129.1, 129.0, 128.4, 128.1, 127.2, 126.9, 124.0, 76.8, 33.6, 25.6. HRMS (ESI). Calcd for $C_{42}H_{36}N_9O_2$ ($[M+H]^+$): *m/z* 698.2986. Found: *m/z* 698.2995.

2-[Bis(5,6-diphenyl-1,2,4-triazin-3-yl)amino]-3-[(4*S*)-4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine 1-oxide (13c) Compound was prepared from 3-[(4*S*)-4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine-2-amine 1-oxide (**12c**) (243 mg, 1.1 mmol), purified by silica gel chromatography (CH_2Cl_2/MeOH, 30:1) and crystallized from hexanes/EtOAc; yield 42% (143 mg); mp 142–144°C; $[\alpha]_D^{20}$ = -21.8 (*c* 0.61, CH_2Cl_2); IR (KBr): 3057, 2958, 1651, 1519, 1489, 1398, 1367, 1282, 1064, 759, 696 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.43 (dd, 1H, *J* = 1.2 Hz, *J* = 6.8 Hz), 7.95 (dd, 1H, *J* = 1.2 Hz, *J* = 8.8 Hz), 7.54–7.47 (m, 9H), 7.40–7.33 (m, 10H), 7.24–7.20 (m, 2H), 4.19 (t, 1H, *J* = 7.6 Hz), 3.94–3.85 (m, 2H), 1.52–145 (m, 1H), 0.64 (d, 3H, *J* = 6.8 Hz), 0.60 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 159.0, 158.9, 158.3, 156.7, 156.6, 153.9, 153.8, 145.7, 141.2, 135.6, 135.5, 135.4, 130.5, 130.4, 130.1, 130.0, 129.4, 129.3, 129.2, 129.1, 128.4, 128.2, 128.1, 127.2, 126.8, 123.9, 72.9, 70.0, 32.4, 18.3, 18.0. HRMS (ESI). Calcd for $C_{41}H_{34}N_9O_2$ ($[M+H]^+$): *m/z* 684.2830. Found: *m/z* 684.2836.

Procedure for the reaction of 3-chloro-5,6-diphenyl-1,2,4-triazine (7b) with (4,5-dihydro-1,3-oxazol-2-yl) pyridine-2-amine 1-oxides in the absence of K_2CO_3

The mixture of 3-chloro-5,6-diphenyl-1,2,4-triazine (**7b**, 267 mg, 1 mmol) and 3-[(4*S*)-4-alkyl/aryl-4,5-dihydro-1,3-oxazol-2-yl]pyridine-2-amine 1-oxide (**12a** or **12b**, 1.1 mmol) in DMF (7 mL) was heated at 50°C for 24 h. The solvent was evaporated under vacuum and the products were isolated by silica gel chromatography (CH_2Cl_2/MeOH, 30:1).

2-(5,6-Diphenyl-1,2,4-triazin-3-ylamino)-3-[(4*S*)-4-*tert*-butyl-4,5-dihydrooxazol-2-yl]pyridine 1-oxide (3a) Compound was prepared from 3-[(4*S*)-4-*tert*-butyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine-2-amine 1-oxide (**12a**, 259 mg, 1.1 mmol); yield 15% (105 mg); mp 98–100°C; $[\alpha]_D^{20}$ = -30.1 (*c* 1.27, CH_2Cl_2); IR (SnZe): 3061, 2955, 1645, 1504, 1360, 1190, 1058, 696 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.59 (br s, 1H), 8.40 (dd, 1H, *J* = 1.2 Hz, *J* = 6.4 Hz), 7.81 (dd, 1H, *J* = 1.2 Hz, *J* = 8.0 Hz), 7.55–7.51 (m, 4H), 7.40–7.29 (m, 6H), 7.08 (dd, 1H, *J* = 6.4 Hz, *J* = 8.0 Hz), 4.05–4.03 (m, 2H), 3.75 (t, 1H, *J* = 9.4 Hz), 0.83 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 160.1, 156.8, 155.7, 152.6, 144.7, 139.9, 135.5, 135.3, 130.6, 129.9, 129.3, 128.9, 128.4, 128.3, 127.6, 118.1, 117.1, 75.8, 68.9, 33.6, 25.8. HRMS (ESI). Calcd for $C_{27}H_{27}N_6O_2$ ($[M+H]^+$): *m/z* 467.2190. Found *m/z* 467.2190.

2-(5,6-Diphenyl-1,2,4-triazin-3-ylamino)-3-[(4*S*)-4-phenyl-4,5-dihydrooxazol-2-yl]pyridine 1-oxide (3b) Compound was prepared from 3-[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine-2-amine 1-oxide (**12b**, 279 mg, 1.1 mmol); yield 10% (29 mg); mp 114–115°C; $[\alpha]_D^{20}$ = -16.2 (*c* 0.49, CH_2Cl_2); IR (SnZe): 3059, 2918, 1643, 1600, 1579, 1487, 1390, 1193, 1060, 694 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.01 (br s, 1H), 8.59 (dd, 1H, *J* = 1.4 Hz, *J* = 6.4 Hz), 7.85 (dd, 1H, *J* = 1.4 Hz, 8.0 Hz), 7.46–7.36 (m, 7H), 7.33–7.32 (m, 4H), 7.24–7.21 (m, 3H), 7.11–7.09 (m, 2H), 5.22 (dd, 1H, *J* = 8.8 Hz, *J* = 10.4 Hz), 4.61 (dd, 1H, *J* = 8.8 Hz, *J* = 10.4 Hz), 3.76 (t, 1H, *J* = 8.8 Hz); ^{13}C NMR ($CDCl_3$): δ 161.8, 156.8, 156.0, 152.9, 144.3, 141.1, 139.5, 135.3, 135.1, 130.8, 129.8, 129.3, 129.1, 128.7, 128.4, 128.3, 128.1, 127.6, 126.4, 118.0, 74.5, 69.8. HRMS (ESI). Calcd for $C_{29}H_{23}N_6O_2$ ($[M+H]^+$): *m/z* 487.1877. Found: *m/z* 487.1880.

3-[(2*S*)-1-Chloro-3,3-dimethylbutan-2-ylcarbamoyl]-2-(5,6-diphenyl-1,2,4-triazin-3-ylamino)pyridine 1-oxide (14a) Compound was prepared from 3-[(4*S*)-4-*tert*-butyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine-2-amine 1-oxide (**12a**, 259 mg, 1.1 mmol); yield 48% (255 mg);

mp 128–130°C; $[\alpha]_D^{20}$ = +11.9 (*c* 0.65, CH_2Cl_2); IR (SnZe): 3059, 2964, 1660, 1573, 1504, 1479, 1242, 1060, 696 cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.89 (br s, 1H), 8.36 (d, 1H, *J* = 6.4 Hz), 7.76 (d, 1H, *J* = 7.6 Hz), 7.52–7.51 (m, 2H), 7.40–7.27 (m, 8H), 7.13–7.09 (m, 2H), 4.16–4.03 (m, 1H), 3.65 (dd, 1H, *J* = 3.6 Hz, *J* = 11.6 Hz), 3.46 (dd, 1H, *J* = 4.8 Hz, 12.0 Hz), 0.84 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 157.7, 157.6, 153.3, 142.4, 138.9, 135.4, 134.9, 130.9, 130.0, 129.2, 129.1, 128.6, 128.4, 128.3, 128.3, 119.7, 58.4, 45.1, 35.1, 26.9. HRMS (ESI). Calcd for $C_{27}H_{28}N_6O_2Cl$ ($[M+H]^+$): *m/z* 503.1957. Found: *m/z* 503.1952.

3-[(*S*)-2-Chloro-1-phenylethylcarbamoyl]-2-(5,6-diphenyl-1,2,4-triazin-3-ylamino)pyridine 1-oxide (14b) Compound was prepared from 3-[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine-2-amine 1-oxide (**12b**, 279 mg, 1.1 mmol); yield 48% (260 mg); mp 157–158°C; $[\alpha]_D^{20}$ = +31.5 (*c* 0.5, CH_2Cl_2); IR (SnZe): 3059, 1651, 1575, 1504, 1483, 1386, 1244, 1062, 694 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.98 (br s, 1H), 9.15 (d, 1H, *J* = 8.8 Hz), 8.56 (dd, 1H, *J* = 1.6 Hz, *J* = 6.4 Hz), 7.57 (dd, 1H, *J* = 1.6 Hz, *J* = 8.0 Hz), 7.43–7.34 (m, 9H), 7.33–7.27 (m, 4H), 7.21–7.15 (m, 3H), 5.18–5.07 (m, 1H), 3.71–3.69 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 164.1, 157.2, 157.1, 153.5, 142.5, 138.8, 137.9, 135.3, 134.7, 131.0, 130.0, 129.4, 129.2, 128.8, 128.7, 128.4, 128.3, 128.2, 126.6, 126.4, 119.0, 54.5, 47.2. HRMS (ESI). Calcd for $C_{29}H_{24}N_6O_2Cl$ ($[M+H]^+$): *m/z* 523.1643. Found: *m/z* 523.1642.

General procedure for the catalytic enantioselective Henry reaction

A mixture of $Cu(OAc)_2{\cdot}H_2O$ (5 mg, 0.025 mmol, 5 mol%) and ligand (0.025 mmol, 5 mol%) in anhydrous 2-propanol (2 mL) 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 mixture was stirred at room temperature for 4 days. Than the solvent was evaporated under reduced pressure and the product was isolated by column chromatography. All spectroscopic data of the nitroaldol adducts were in good agreement with those reported previously [1].

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