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ORIGINAL PAPER

Chiral pyridine oxazoline and 1,2,4-triazine oxazoline ligands incorporating electron-withdrawing substituents and their application in the Cu-catalyzed enantioselective nitroaldol reaction

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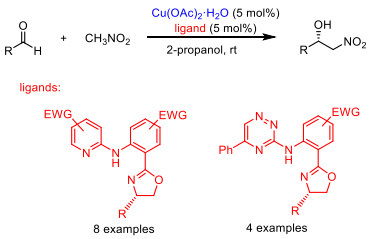
Abstract

Eight pyridine-containing and four 1,2,4-triazine-containing chiral oxazoline ligands incorporating electron-withdrawing substituents have been synthesized by two-step route including Buchwald–Hartwig amination. Enantio-inducing activity of the ligands has been assessed in the copper-catalyzed asymmetric nitroaldol reactions and the influence of the electron-withdrawing substituents on the ligands' activity has been investigated.

Graphical abstract



Keywords Asymmetric catalysis · Chiral oxazoline ligands · Enantioselective nitroaldol reaction · 1,2,4-triazine · Pyridine · Buchwald–Hartwig amination

Introduction

Metal-based asymmetric catalysis has proven to be a useful tool for preparation of enantiomerically pure compounds [1, 2]. Since steric and electronic properties of metal catalysts, and consequently enantio-selectivity of asymmetric processes are determined by organic ligands, the development of efficient chiral ligands is still a major topic in the area of asymmetric catalysis. Chiral oxazoline derivatives constitute a huge group of versatile chiral ligands that utility was proved in diverse metal-catalyzed asymmetric reactions including cyclopropanations, hydrosilylations, hydrogenations, allylic alkylations, diethylzinc additions to aldehydes, Diels–Alder reactions, and nitroaldol reaction [3–8]. The asymmetric nitroaldol reaction is a powerful tool in the synthesis of chiral *β*-nitro-alcohols, which are useful starting materials in the synthesis of diverse bifunctional compounds [9]. Among the various transition metals tested as catalysts in the nitroaldol reaction, copper showed the highest catalytic activity. It forms highly active complexes not only with oxazoline ligands but also with a wide variety of chiral ligands, such as amine-based ligands, Schiff base-based ligands, salen-based ligands, amino alcohols-based ligands, salalen-based ligands, which have been recently summarized in two review papers [10, 11]. According to our ongoing research project focusing on the synthesis and application of ligands that combine in their structures chiral oxazoline and six-membered aza-heteroaromatic rings, we have examined ligands with 1,2,4-triazine **1a**-**1d** (ligands

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type **1**), pyridine, pyrimidine, and pyrazine ring **2a**-**2c**, **3a**-**3c** (ligands type **2** and **3**) (Fig. 1) [12–17]. In the ligands, the chiral oxazoline ring and the aza-heteroaromatic ring are linked by *N*-phenylamine unit. The ability of the ligands to induce enantio-selectivity has been assessed in the copper-catalyzed asymmetric nitroaldol reaction of nitromethane with a variety of aromatic and aliphatic aldehydes. This study revealed that the ligands with 1,2,4-triazine scaffold **1a**-**1d** exhibit significantly higher enantio-inducing activity than the ligands **2a**-**2c** and **3a**-**3c** possessing other six-membered aza-heteroaromatic ring.

Among them, the ligands **1a** and **1d** appeared to be the most active. Asymmetric Henry reaction catalyzed by ligand **1a** gave the nitro-alcohols with enantiomeric excess up to 82% [12] while utility of **1d** as catalyst allowed to obtain the products with optical purity up to 92% and yield up to 95% [13]. For comparison, the highest optical purity obtained in the presence of ligands **2a**-**2c** incorporating the pyridine ring was 34% [14]. Moderate enantio-selectivity up to 67% was observed in reactions catalyzed by ligands **3a**-**3c** [14]. It is suggested that two factors can be responsible for the difference in activity of the 1,2,4-triazine-containing ligands **1a**-**1c** and ligands possessing other six-membered aza-aromatic rings **2a**-**2c** and **3a**-**3c** [16]. The complexes formed between ligands of types **1**, **2**, and **3** and copper ions were not stable and an attempt to isolate them and to study their structures by X-ray diffraction analysis failed. The structures of the complexes were proposed by us on the basis of UV, MS, ^{1}H NMR study and theoretical calculations [16]. Ligands of type **1** that are more sterically hindered due to the presence of substituents in the 1,2,4-triazine ring tend to form slightly distorted tetrahedral quaternary complexes with the Cu(I) ion. Less bulky ligands of type **2** and **3** with an unsubstituted six-membered heterocyclic rings probably prefer to form square planar complexes with Cu(II) ions (Fig. 2) [16].

The difference in activity of type **1**, type **2**, and type **3** ligands can also be explained by considering the acidity of the copper ion in the **1**-Cu, **2**-Cu, and **3**-Cu complexes they

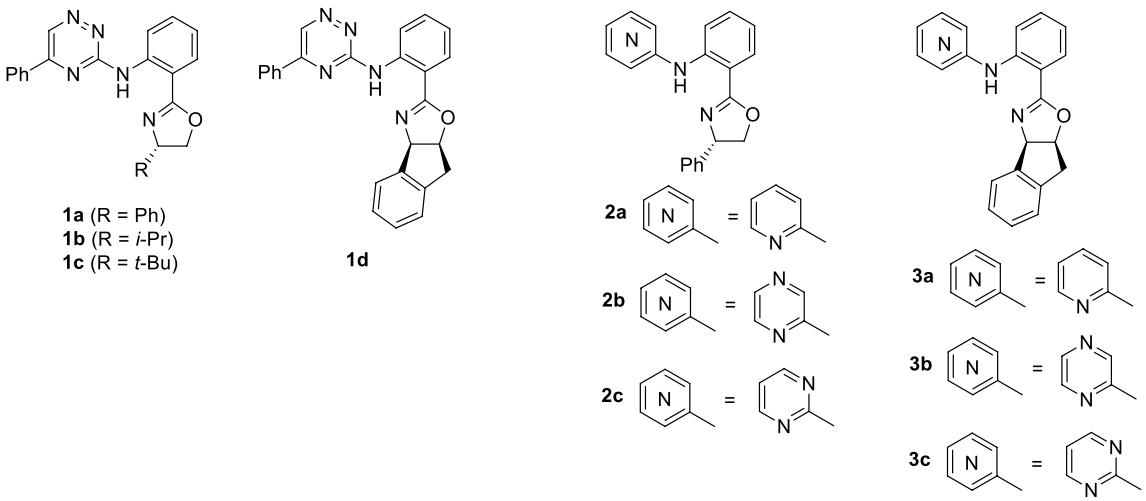


Fig. 1 Previously investigated chiral oxazoline ligands with six-membered aza-heteroaromatic ring

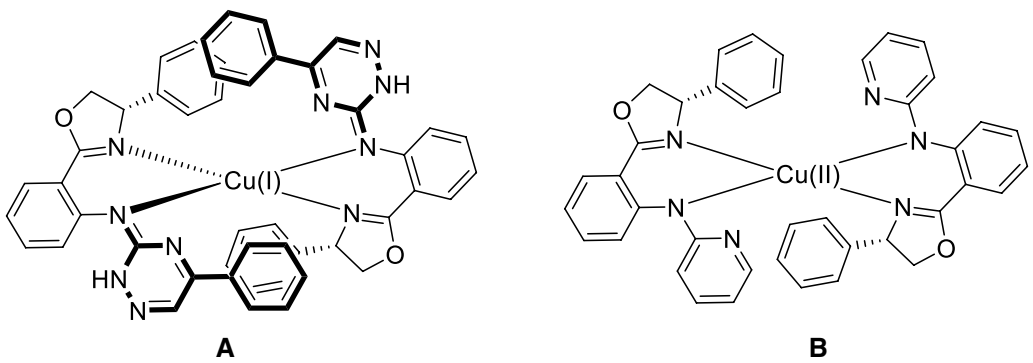
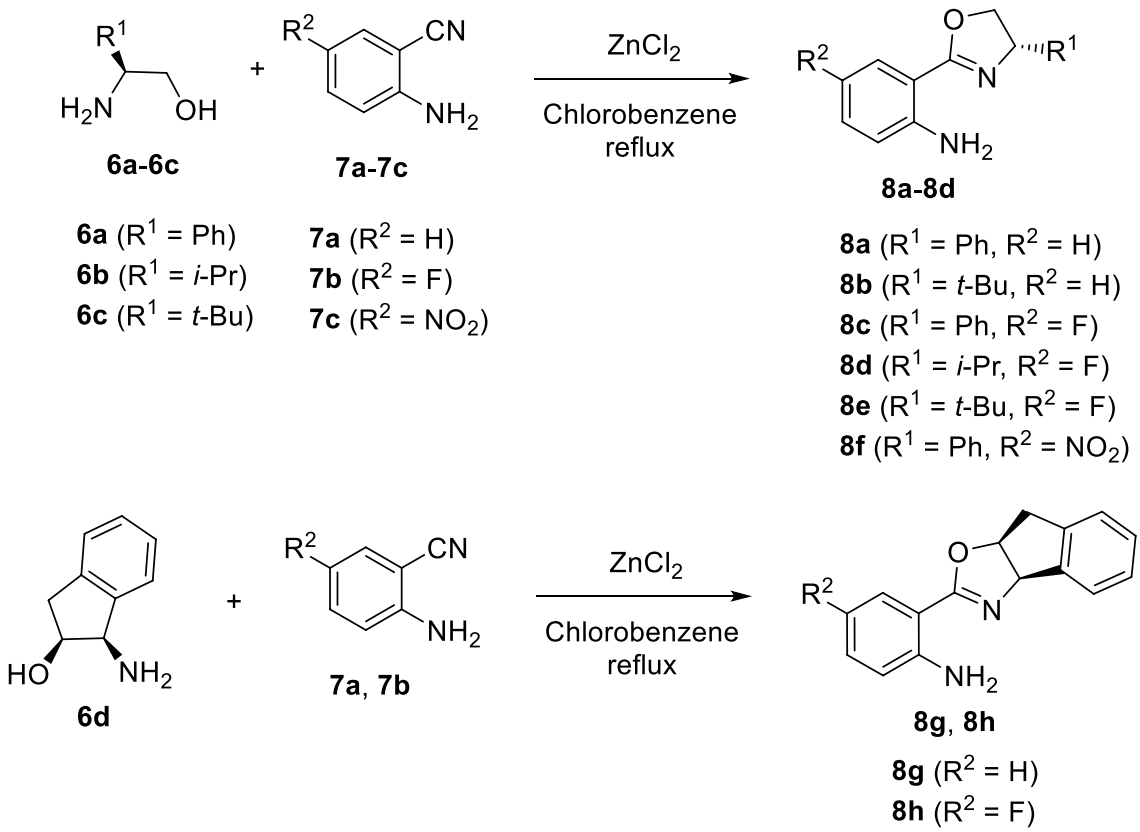


Fig. 2 Proposed structures of copper complexes of triazine–oxazoline ligands (A) and pyridine oxazoline ligands (B) [16]

Scheme 1



form. The more electron-withdrawing character of 1,2,4-triazine ring makes the copper ion in the **1**-Cu complex more acidic, which provides better activation of the coordinating aldehyde. Type **2** and **3** ligands with heterocyclic rings of weaker electron-withdrawing character provide less activation [16]. Taking the above into account, introduction of electron-withdrawing group to the structures of ligands **2a**-**2c** and **3a**-**3c** should result in increase of their enantio-inducing activity. To investigate which of the above-mentioned factors has a decisive influence on the activity of ligands **1a**-**1c**, **2a**-**2c**, and **3a**-**3c**, new pyridine oxazoline ligands **4a**-**4h**, analogous to ligands **2a** and **3a**, whose structures were modified by introducing an electron-withdrawing group, were synthesized and examined in an enantioselective nitroaldol reaction.

This studies are in line with still growing interest in pyridine-containing oxazoline ligands, the utility of which has recently been proved in many new asymmetric processes, e.g., aza-Wacker-type cyclization and C–H silylation [18–23]. Synthesis of new 1,2,4-triazine oxazoline ligands **5a**-**5d** incorporating electron-withdrawing substituents was also performed and their activity in asymmetric nitroaldol reaction was investigated and compared to the activity of their counterparts **1a**-**1d** without electronegative substituents. Herein we describe the results of the work.

Results and discussion

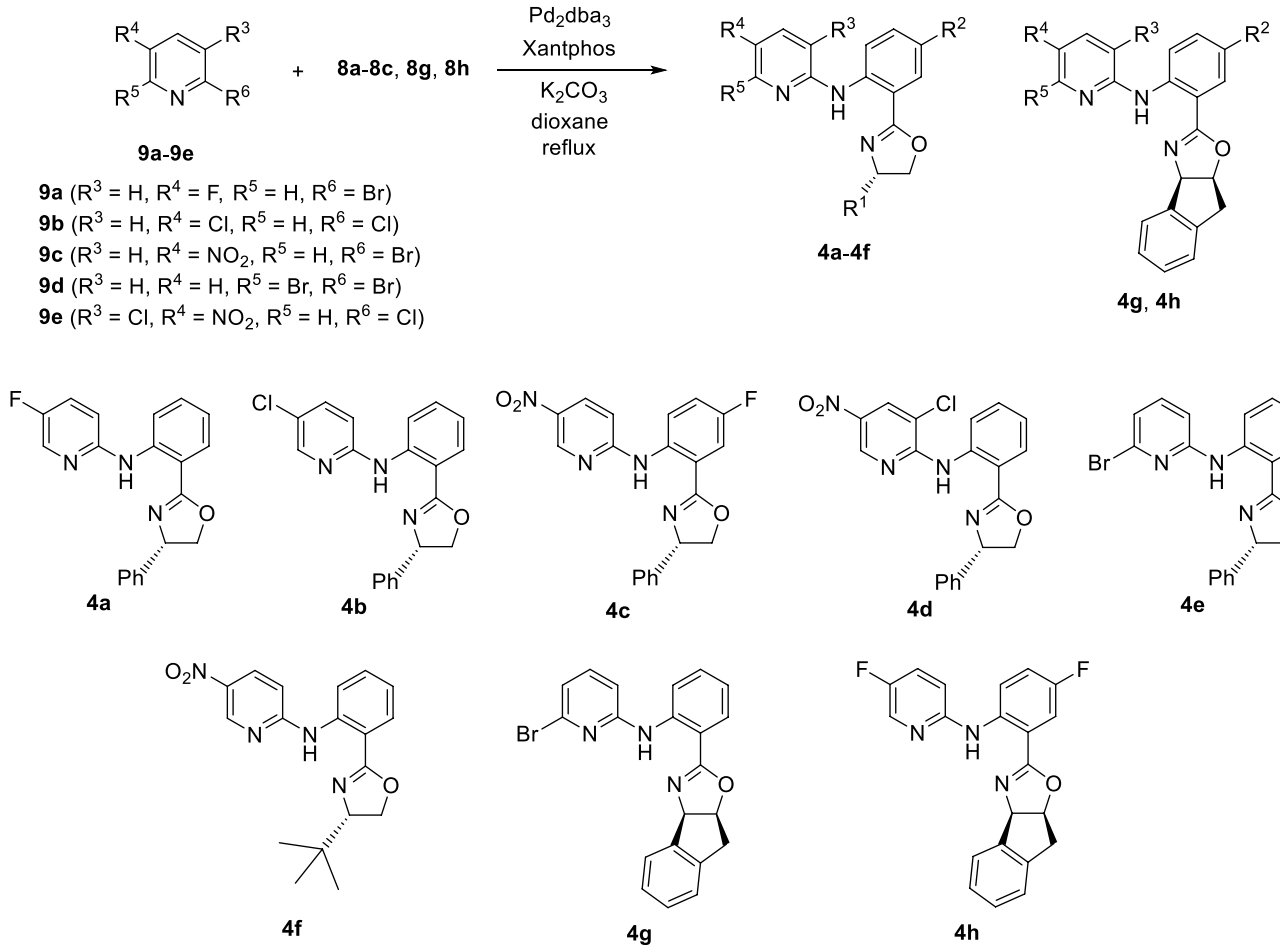
Synthesis of ligands

Previously elaborated two-step synthetic route was adopted to synthesize ligands **4a**-**4h** and **5a**-**5d** [12]. The synthesis began with condensation of enantiomerically pure amino alcohols **6a**-**6d** with the CN group of 2-aminobenzonitrile (**7a**) or its 5-fluoro-(**7b**) or 5-nitro-(**7c**) derivative to yield chiral 2-(*o*-aminophenyl)oxazolines **8a**-**8h** (Scheme 1).

The condensation reaction was run in the presence of threefold excess of $ZnCl_2$ which allowed to shorten the reaction time and gain better yield of the products in comparison to experiments run in the presence of catalytic amount of the catalyst. Subsequently, the Pd-catalyzed Buchwald–Hartwig amination of halopyridine derivatives **9a**-**9e** with 2-(*o*-aminophenyl)oxazolines **8a**-**8c**, **8g**, and **8h** was conducted to obtain the final ligands **4a**-**4h** (Scheme 2).

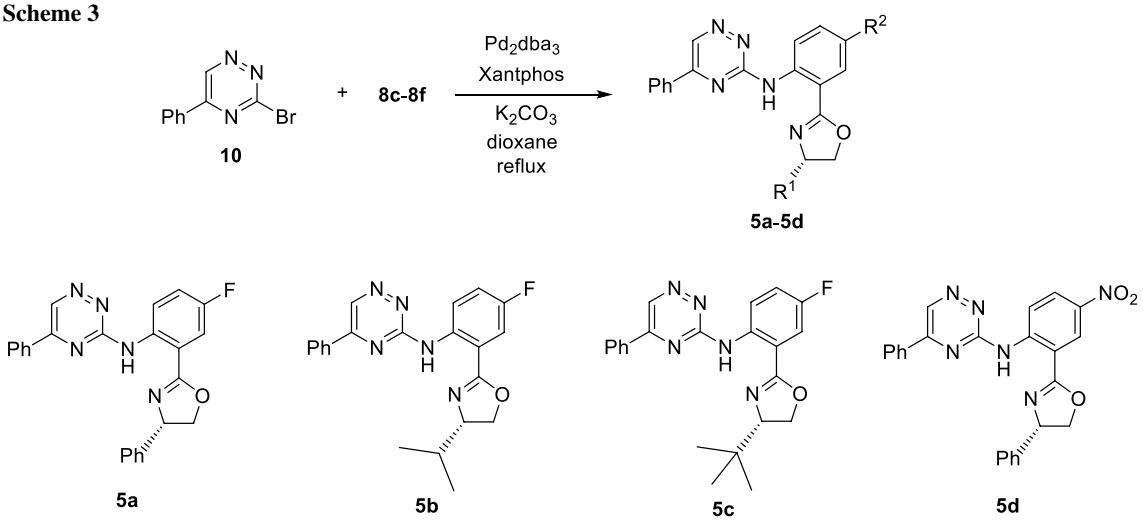
The synthetic approach allowed to obtain ligands **4a**, **4b**, and **4d**-**4g** having the electron-withdrawing

Scheme 2



substituents in the pyridine ring and ligands **4c** and **4h** with electron-withdrawing substituents in the pyridine and the phenyl ring of the phenylamine linkage. Similarly, 3-bromo-5-phenyl-1,2,4-triazine (**10**) was subjected to C–N palladium-coupling with 2-(*o*-aminophenyl)oxazolines **8c**-**8f** yielding 1,2,4-triazine ligands **5a**-**5d** (Scheme 3).

Scheme 3



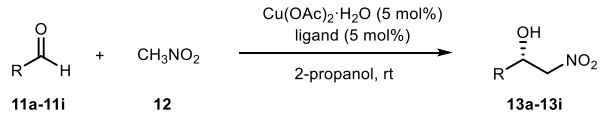
In the structures of 1,2,4-triazine-containing ligands **5a**-**5d,** the fluorine or the nitro group is placed in the phenylamine linkage. Synthesis of the counterpart of the highly active ligand **1d** incorporating the indane unit and fluorine atom in the phenylamine linkage was also undertaken. Unfortunately the ligand appeared highly insoluble in the solvents commonly used for purification and its isolation in chemically pure form did not succeed.

Enatio-selective nitroaldol reaction

With the chiral oxazoline ligands **4a**-**4h** and **5a**-**5d** in hand, we attempted to examine their enantio-inducing abilities in the copper-catalyzed asymmetric addition of nitromethane (**12**) to variety of aldehydes **11a**-**11i**. To perform the nitro-aldol reactions, the conditions previously optimized for ligands **1**, **2**, and **3** were adopted. Thus, the reactions were carried out in the presence of 5 mol% of ligand and $Cu(OAc)_2 \cdot H_2O$ as pre-catalyst in 2-propanol at room temperature in the absence of any base. Yields and optical purities of the nitro-alcohols thus obtained are summarized in Table 1.

The results show that the ligands **4a**-**4g** do not exhibit enantio-inducing activity (Table 1, entries 1–9). The optical purity of the nitro-alcohols obtained in reactions catalyzed by these ligands did not exceed 29%. Ligand **4h** appeared the most active among the pyridine oxazoline ligands. The highest enantiomeric excess, 48 and 71% were obtained in reactions catalyzed by ligand **4h** what should be owed to the presence of the indane unit (Table 1, entries 10 and 11). Placement of a bromine atom in the C-6 position of the pyridine ring in ligands **4e** and **4g** makes the ligands highly inactive (Table 1, entries 7 and 9), although in the presence of the ligand **4e,** the highest reaction rate was achieved. Both ligands **4g** and the most active pyridine-containing ligand **4h** possess indane unit in their structures, but they differ in activity (Table 1, entries 9 and 10), which proves that the presence of the bromine atom in the C-6 position of the pyridine ring has unfavorable influence on the ligands activity. Comparing the results described above to the activity of previously investigated ligands types **2** and **3**, it can be seen that presence of electron-withdrawing substituents in the structures of ligands **4a**-**4h** did not improve the pyridine oxazoline ligands enantio-inducing ability [14]. The enantio-selectivities obtained in nitro-aldol reactions carried out in the presence of type **2** ligands were in the range of 4–28%. Ligands of type **3** having an indane system in the structure were showing better enantio-differentiating properties, and so the enantio-selectivity induced by them reached 64% in reactions with 2-substituted benzaldehydes [14]. This tendency is also observed for the activity of ligands **4a**-**4h** possessing electron-withdrawing substituents. Conformationally rigid ligand **4h** with indane system shows higher activity than ligands **4a**-**4g** having flexible substituent in the oxazoline ring. Ligands **5a**-**5c** are 1,2,4-triazine oxazoline ligands that possess the fluorine atom in the phenyl-amine unit, but they differ in the substituent in the oxazoline ring. In the presence of ligand **5a** with phenyl substituent in the oxazoline ring, the highest yield and enantiomeric excess, 96 and 87%, respectively, were achieved in reaction of 2-chlorobenzaldehyde (Table 1, entry 18). In contrast, ligand **5a** showed the lowest enantio-inducing activity in addition of nitromethane to 3-chlorobenzaldehyde (Table 1, entry 17). In this case, the product was formed in the yield of 17% and enantiomeric excess of 45%. Ligand **5b** with isopropyl substituent in the oxazoline ring appeared to be a good catalyst in term of accelerating the reaction rate, but it shows poor enantio-inducing ability in the range of 32–49% (Table 1, entries 21–25). The three isomeric nitro-benzaldehydes underwent the catalyzed by **5b** addition of nitro-methane in excellent yield of 94–99% (Table 1, entries 21–23). Moderate yield was observed in the reactions of 2-bromo- and 2-chlorobenzaldehydes, 70 and 73%, respectively (Table 1, entries 24 and 25). Replacement of a fluorine atom with a nitro group in ligand **5d** leads to a decrease in yield of the nitro-aldol reaction, while enantiomeric excess remained on a similar level in most cases in comparison to the results obtained in the presence of ligand **5a** (Table 1, entries 27–31). Only in reaction of 2-bromobenzaldehyde significantly reduced yield and enantiomeric excess were observed. Utility of ligand **5c** possessing *tert*-butyl group in the oxazoline ring in the reaction of 4-nitrobenzaldehyde allowed to achieve optical purity of only 24% and yield of 68% (Table 1, entry 26). That makes this ligand not promising candidate for catalyst in asymmetric nitro-aldol reaction. The presence of the fluorine atom in ligand **5a** had no effect on the ligand enantio-inducing activity in comparison to its previously investigated counterpart **1a** [12], whereas introduction of the nitro-substituent (ligand **5d**) negatively influenced the reaction ratio. Similarly, the presence of fluorine in structures **5b** and **5c** did not make them good candidates for ligands in asymmetric nitroaldol reaction. The 1,2,4-triazine oxazoline ligands **5a**-**5d** show much better enantio-inducing activity than the pyridine oxazoline ligands **4a**-**4g**. Only the **4h** ligand with indane unit showed activity similar to that of the 1,2,4-triazine oxazoline **5a** and **5d** ligands in reactions with 2-bromo- and 2-chlorobenzaldehydes, although the yields observed in the reactions with **4h** were lower. The higher activity of ligand **4h** is due to the presence of a conformationally rigid indane system rather than pyridine in its structure. Introduction of electron-withdrawing substituents to pyridine-containing oxazoline ligands did

Table 1 Screening of ligands **4a**-**4h** and **5a**-**5d** in the asymmetric nitro-aldol reaction



11a-11i **12** **13a-13i**

Entry	R	Aldehyde	Ligand	Product	Yield[a]/%	Ee[b]/%
1	4-$NO_2C_6H_4$	**11a**	**4a**	**13a**	65	13 (*S*)
2	2-BrC_6H_4	**11b**	**4a**	**13b**	46	13 (*S*)
3	4-$NO_2C_6H_4$	**11a**	**4b**	**13a**	63	racemate
4	2-BrC_6H_4	**11b**	**4b**	**13b**	37	29 (*S*)
5	4-$NO_2C_6H_4$	**11a**	**4c**	**13a**	65	12 (*S*)
6	4-$NO_2C_6H_4$	**11a**	**4d**	**13a**	41	13 (*S*)
7	4-$NO_2C_6H_4$	**11a**	**4e**	**13a**	75	racemate
8	4-$NO_2C_6H_4$	**11a**	**4f**	**13a**	46	racemate
9	4-$NO_2C_6H_4$	**11a**	**4g**	**13a**	20	8 (*R*)
10	4-$NO_2C_6H_4$	**11a**	**4h**	**13a**	52	48 (*R*)
11	2-BrC_6H_4	**11b**	**4h**	**13b**	45	71 (*R*)
12	4-$NO_2C_6H_4$	**11a**	**5a**	**13a**	69	34 (*S*)
13	2-BrC_6H_4	**11b**	**5a**	**13b**	89	64 (*S*)
14	3-$NO_2C_6H_4$	**11c**	**5a**	**13c**	80	42 (*S*)
15	2-$NO_2C_6H_4$	**11d**	**5a**	**13d**	73	66 (*S*)
16	4-ClC_6H_4	**11e**	**5a**	**13e**	53	55 (*S*)
17	3-ClC_6H_4	**11f**	**5a**	**13f**	17	45 (*S*)
18	2-ClC_6H_4	**11g**	**5a**	**13g**	96	87 (*S*)
19	2-$MeOC_6H_4$	**11h**	**5a**	**13h**	83	62 (*S*)
20	1-naphthyl	**11i**	**5a**	**13i**	37	39 (*S*)
21	4-$NO_2C_6H_4$	**11a**	**5b**	**13a**	94	35 (*S*)
22	3-$NO_2C_6H_4$	**11c**	**5b**	**13c**	99	32 (*S*)
23	2-$NO_2C_6H_4$	**11d**	**5b**	**13d**	94	49 (*S*)
24	2-BrC_6H_4	**11b**	**5b**	**13b**	70	47 (*S*)
25	2-ClC_6H_4	**11g**	**5b**	**13g**	73	42 (*S*)
26	4-$NO_2C_6H_4$	**11a**	**5c**	**13a**	68	24 (*S*)
27	4-$NO_2C_6H_4$	**11a**	**5d**	**13a**	86	46 (*S*)
28	2-BrC_6H_4	**11b**	**5d**	**13b**	48	49 (*S*)
29	3-$NO_2C_6H_4$	**11c**	**5d**	**13c**	88	39 (*S*)
30	2-$NO_2C_6H_4$	**11d**	**5d**	**13d**	64	65 (*S*)
31	2-ClC_6H_4	**11g**	**5d**	**13g**	73	70 (*S*)

All reactions were performed on a 0.5 mmol scale with 5 mol % of ligand and 5 mol % of $Cu(OAc)_2·H_2O$ in 2 cm^3 of 2-propanol at room temperature for 98 h

[a]Yields of isolated products

[b]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 [21–24]

not result in increase of the ligand activity in comparison to the previously investigated ligands **2** and **3** without any electron-withdrawing group in the structure [14]. The findings described above indicate that the difference in the activity between 1,2,4-triazine oxazoline and pyridine oxazoline ligands is not a result of the more electron-withdrawing character of 1,2,4-triazine ring, as it was postulated [16]. It arises rather from the formation of different complexes with copper ions formed by the two types of ligands, the structures of which were proposed previously [16]. The more electron-withdrawing character of 1,2,4-triazine ring appeared less significant.

Conclusion

In conclusion, we have obtained eight new pyridine-containing **4a**-**4h** and four 1,2,4-triazine-containing **5a**-**5d** chiral oxazoline ligands incorporating electron-withdrawing groups. To determine the influence of the substituents on catalytic and enantio-inducing activity of the ligands, they have been employed in copper-catalyzed asymmetric nitro-aldol reaction. It has been found that 1,2,4-triazine-containing ligands **5a**-**5d** exhibit better activity that pyridine-containing ligands **4a**-**4g**. Only ligand **4h** shows activity comparable to that of triazine-oxazoline ligands **5a**-**5d**. The activity of ligands **4a**-**4h** and **5a**-**5d** appeared similar to the activity of their previously investigated counterparts without electron-withdrawing substituents [12–14]. The introduction of an electron-withdrawing substituent into the structures of both types of ligands, triazine-oxazoline and pyridine oxazoline ligands, did not result in an increase in their enantio-differentiating properties. It has been proven that the more electron-withdrawing character of 1,2,4-triazine ring is not responsible for the better enantio-inducing ability of 1,2,4-triazine oxazoline ligands. The difference in activity of 1,2,4-triazine oxazoline and pyridine oxazoline ligands must be due to the difference in the structures of the copper complexes formed by the ligands (Fig. 2) [16].

Experimental

^{1}H spectra were determined at 400 MHz with a Varian 400 MR spectrometer. Chemical shifts (δ) were reported in part per million from tetra-methyl-silane with the solvent resonance as the internal standard. Coupling constants are given as absolute values expressed in Hertz. Mass spectra were obtained using LTQ Orbitrap Velos (Thermo Scientific) spectrometer. Melting points were determined on Boethius melting point apparatus. Optical rotation values were measured at room temperature with a Perkin-Elmer polarimeter. The ee values were determined by HPLC analysis using a chiral stationary phase column (Chiralcel OD-H), and elution with isopropanol–hexanes. Thin-layer chromatography (TLC) was carried out on aluminum sheets pre-coated with silica gel 60 F254 (Merck). Column chromatography separations were performed using Merck Kieselgel 60 (0.040–0.060 mm). Solvents were dried according to standard procedures. 3-Bromo-5-phenyl-1,2,4-triazine (**10**) was synthesized according to literature procedures [28]. Oxazolines 2-[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (**8a**), 2-[(4*S*)-4-*tert*-butyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (**8b**) [29], 4-fluoro-2-[(4*S*)-4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl]-aniline (**8d**) [30], and 2-[(3a*R*,8a*S*)-8,8a-dihydro-3a*H*-indeno[1,2-d]oxazol-2-yl]aniline (**8g**) [31], were synthesized by us previously and their physical and spectroscopic data are with agreement with the published ones.

General procedure for the synthesis of 2-(*o*-aminophenyl)oxazolines 8a-8h

An oven-dried two-necked flask was washed with argon and charged with 118 mg 2-aminobenzonitrile (1 mmol) or 136 mg 2-amino-5-fluorobenzonitrile (1 mmol) or 163 mg 2-amino-5-nitrobenzonitrile (1 mmol), the appropriate amino alcohol (1.5 mmol), 405 mg freshly flame dried $ZnCl_2$ (3 mmol), and 10 cm^3 anhydrous chlorobenzene. 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 ethyl ether and purified by flash column chromatography on silica gel.

2-[(4*S*)-4-Phenyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (8a) Compound **8a** was prepared from 118 mg 2-aminobenzonitrile (**7a**, 1 mmol) and 205 mg *S*-phenylglycinol (**6a**, 1.5 mmol). White crystals; yield 203 mg (85%). All the physical and spectroscopic data are with agreement with the ones published in Ref. [29].

2-[(4*S*)-4-*tert*-Butyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (8b) Compound **8b** was prepared from 118 mg 2-aminobenzonitrile (**7a**, 1 mmol) and 175 mg *S*-*tert*-leucinol (**6c**, 1.5 mmol). White crystals; yield 213 mg (98%). All the physical and spectroscopic data are with agreement with the ones published in Ref. [29].

4-Fluoro-2-[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]-aniline (8c, $C_{15}H_{13}FN_2O$) Compound **8c** was prepared from 136 mg 2-amino-5-fluorobenzonitrile (**7b**, 1 mmol) and 205 mg *S*-phenylglycinol (**6a**, 1.5 mmol) and purified by column chromatography (CH_2Cl_2/hexane 5:7). White crystals; yield 206 mg (82%); m.p.: 88–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.46$ (dd, $J = 9.6$, 3.2 Hz, 1H), 7.38–7.35 (m, 2H), 7.31–7.29 (m, 3H), 7.02–6.97 (m, 1H), 6.67 (dd, $J = 8.8$, 4.4 Hz, 1H), 5.98 (br.s, 2H), 5.46 (dd, $J = 10.0$, 8.4 Hz, 1H), 4.73 (dd, $J = 10.0$, 8.4 Hz, 1H) 4.14 (t, $J = 8.4$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.2$ (d, $J_{C,F} = 2.6$ Hz, C=N), 154.0 (d, $J_{C,F} = 232.2$ Hz, C-F), 145.2, 142.4, 128.7, 127.6, 126.6, 119.8 (d, $J_{C,F} = 23.0$ Hz, C_{ortho}–CF), 116.7 (d, $J_{C,F} = 7.3$ Hz, C_{meta}–CF), 115.1 (d, $J_{C,F} = 23.6$ Hz, C_{ortho}–CF), 108.7 (d, $J_{C,F} = 7.4$ Hz, C_{meta}–CF), 73.2, 70.3 ppm; HRMS (ESI): *m/z* calcd for $C_{15}H_{14}FN_2O$ ($[M + H]^+$)

257.1082, found 257.1084; $[\alpha]_D^{20} = +82.46°$ cm^2 g^{-1} ($c = 0.65$, CH_2Cl_2).

4-Fluoro-2-[(4*S*)-4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl]-aniline (8d) Compound **8d** was prepared from 136 mg 2-amino-5-fluorobenzonitrile (**7b**, 1 mmol) and 155 mg L-valinol (**6b**, 1.5 mmol) and purified by column chromatography (CH_2Cl_2/hexane 5:3.5). White color; yield 208 mg (94%). All the physical and spectroscopic data are with agreement with the ones published in Ref. [30].

4-Fluoro-2-[(4*S*)-4-*tert*-butyl-4,5-dihydro-1,3-oxazol-2-yl]-aniline (8e, $C_{13}H_{17}FN_2O$) Compound **8e** was prepared from 136 mg 2-amino-5-fluorobenzonitrile (**7b**, 1 mmol) and 175 mg *S*-*tert*-leucinol (**6c**, 1.5 mmol) and purified by column chromatography (CH_2Cl_2/hexane 1:1). White crystals; yield 142 mg (60%); m.p.: 71–73 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.37$ (dd, $J = 10.0$, 3.2 Hz, 1H), 6.98–6.92 (m, 1H), 6.66–6.62 (m, 1H), 5.98 (br.s, 2H), 4.28–4.22 (m, 1H), 4.14–4.10 (m, 2H), 0.94 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 162.6$ (d, $J_{C,F} = 2.6$ Hz, C=N), 154.0 (d, $J_{C,F} = 232.1$ Hz, C-F), 145.0, 119.3 (d, $J_{C,F} = 22.8$ Hz, C_{ortho}–CF), 116.5 (d, $J_{C,F} = 7.3$ Hz, C_{meta}–CF), 114.9 (d, $J_{C,F} = 23.8$ Hz, C_{ortho}–CF), 109.2 (d, $J_{C,F} = 7.4$ Hz, C_{meta}–CF), 76.5, 67.0, 33.8, 25.8 ppm; HRMS (ESI): *m/z* calcd for $C_{13}H_{18}FN_2O$ ($[M+H]^+$) 237.1397, found 237.1393; $[\alpha]_D^{20} = +28.04°$ cm^2 g^{-1} ($c = 0.56$, CH_2Cl_2).

4-Nitro-2-[(4*S*)-4-phenyl-4,5-dihydro-1,3-oxazol-2-yl]aniline (8f, $C_{15}H_{13}N_3O_3$) Compound **8f** was prepared from 163 mg 2-amino-5-nitrobenzonitrile (**7c**, 1 mmol) and 205 mg *S*-phenylglycinol (**7a**, 1.5 mmol) and purified by column chromatography (CH_2Cl_2/hexane 5:7) and recrystallized from ethanol. Yellow crystals; yield 240 mg (85%); m.p.: 174–176 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.73$ (d, $J = 2.4$ Hz, 1H), 8.11 (dd, $J = 9.2$, 2.8 Hz, 1H), 7.40–7.28 (m, 5H), 6.69 (d, $J = 9.2$ Hz, 1H), 5.47 (dd, $J = 6.4$, 4.8 Hz, 1H), 4.76 (dd, $J = 10.0$, 8.0 Hz, 1H), 4.21 (t, $J = 8.4$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 163.6$, 153.4, 141.9, 137.1, 128.8, 127.8, 127.8, 127.4, 126.5, 114.9, 107.4, 73.4, 70.3 ppm; HRMS (ESI): *m/z* calcd for $C_{15}H_{14}N_3O_3$ ($[M+H]^+$) 284.1029, found 284.1028; $[\alpha]_D^{20} = -44.02°$ cm^2 g^{-1} ($c = 0.50$, CH_2Cl_2).

2-[(3a*R*,8a*S*)-8,8a-Dihydro-3a*H*-indeno[1,2-*d*]oxazol-2-yl]aniline (8g) Compound **8g** was prepared from 118 mg 2-aminobenzonitrile (**7a**, 1 mmol) and 224 mg (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (**6d**, 1.5 mmol). White crystals; yield 135 mg (54%). All the physical and spectroscopic data are with agreement with the ones published in Ref. [31].

4-Fluoro-2-[(3a*R*,8a*S*)-8,8a-dihydro-3a*H*-indeno[1,2-*d*]--oxazol-2-yl]aniline (8h, $C_{16}H_{13}FN_2O$) Compound **8h** was prepared from 136 mg 2-amino-5-fluorobenzonitrile (**7b**, 1 mmol) and 224 mg (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (**6d**, 1.5 mmol) and purified by column chromatography using CH_2Cl_2 as eluent and recrystallized from ethanol. White crystals; yield 188 mg (70%); m.p.: 151–153 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.51$–7.48 (m, 1H), 7.38 (dd, $J = 9.6$, 2.8 Hz, 1H), 7.27–7.24 (m, 3H), 6.91 (ddd, $J = 9.2$, 8.4, 3.2 Hz, 1H), 5.90 (brs, 2H), 5.78 (d, $J = 8.0$ Hz, 1H), 5.37 (ddd, $J = 8.4$, 7.2, 1.6 Hz, 1H), 3.52–3.46 (m, 1H), 3.37–3.30 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 163.2$ (d, $J_{C,F} = 2.6$ Hz, C=N), 154.0 (d, $J_{C,F} = 232.1$ Hz, C-F), 144.9, 142.1, 139.7, 128.4, 127.4, 125.4, 125.3, 119.4 (d, $J_{C,F} = 22.5$ Hz, C_{ortho}–CF), 116.6 (d, $J_{C,F} = 7.3$ Hz, C_{meta}–CF), 115.0 (d, $J_{C,F} = 23.8$ Hz, C_{ortho}–CF), 109.1 (d, $J_{C,F} = 7.6$ Hz, C_{meta}–CF), 81.4, 77.1, 39.6 ppm; HRMS (ESI): *m/z* calcd for $C_{16}H_{14}FN_2O$ ($[M+H]^+$) 269.1085, found 269.1085; $[\alpha]_D^{20} = -102.3°$ cm^2 g^{-1} ($c = 0.56$, CH_2Cl_2).

General procedure for synthesis of ligands 4a-4h and 5a-5d

An oven-dried three-necked flask was washed with argon and charged with 45.8 mg Pd_2dba_3 (10 mol%), 57.8 mg Xantphos (20 mol%), 2-(4,5-dihydro-1,3-oxazol-2-yl)aniline **8a**-**8h** (0.6 mmol), halopyridine derivative **9a**-**9e** (0.5 mmol) or 3-bromo-5-phenyl-1,2,4-triazine (**10**, 0.5 mmol) and 1.38 g K_2CO_3 (10 mmol). Then, the flask was evacuated and backfilled with argon. Dioxane (10 cm^3) was added through the septum. The mixture was refluxed under Ar for 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 by column chromatography.

2-[2-[(4*S*)-4-Phenyl-4,5-dihydrooxazol-2-yl]-phenylamino]-5-fluoropyridine (4a, $C_{20}H_{16}FN_3O$) Ligand **4a** was obtained from 143 mg **8a** and 88 mg 2-bromo-5-fluoropyridine (**9a**) after 15 h of reflux and purified by column chromatography (CH_2Cl_2/hexanes 5:3.5). White crystals; m.p.: 55–56 °C; yield 166 mg (73%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 11.67$ (s, 1H), 8.70 (d, $J = 8.4$ Hz, 1H), 8.14 (d, $J = 3.2$ Hz, 1H), 7.93 (dd, $J = 8.0$, 1.6 Hz, 1H), 7.47 (dt, $J = 8.8$, 2 Hz, 1H), 7.41–7.30 (m, 5H), 7.27–7.22 (m, 1H), 6.94 (dt, $J = 8.4$, 0.8 Hz, 1H), 6.74 (dd, $J = 8.8$, 3.6 Hz, 1H), 5.53 (dd, $J = 8.8$, 1.2 Hz, 1H), 4.75 (dd, $J = 8.4$, 10.0 Hz, 1H), 4.17 (t, $J = 8.4$ Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 165.3$, 154.5 (d, $J = 245.1$ Hz, C-F), 151.7, 143.0, 142.3, 134.1 (d, $J = 24.4$ Hz, C_{ortho}–CF), 132.6, 129.7, 128.8, 127.6, 126.4, 125.2 (d, $J = 20.5$ Hz, C_{ortho}–CF), 118.9, 116.6, 113.6 (d, $J = 4$ Hz, C_{meta}–CF), 111.0, 73.2, 70.0 ppm; HRMS (ESI): *m/z* calcd for $C_{20}H_{17}FN_3O$

([M + H]$^+$) 334.1350, found 334.1347; $[\alpha]_D^{20} = +363.2°$ cm^2 g^{-1} ($c = 0.53$, CH_2Cl_2).

2-[2-[(4*S*)-4-Phenyl-4,5-dihydrooxazol-2-yl]-phenylamino]-5-chloropyridine (4b, $C_{20}H_{16}ClN_3O$) Ligand **4b** was obtained from 143 mg **8a** and 74 mg 2,5-dichloropyridine (**9b**) after 20 h of reflux. It was purified by column chromatography (CH_2Cl_2/hexanes 5:3.5) and recrystallized from ethanol. White crystals; yield 121 mg (69%); m. p.: 87–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 11.75$ (s, 1H), 8.74 (d, $J = 8.4$ Hz, 1H), 8.22 (d, $J = 3.2$ Hz, 1H), 7.93 (dd, $J = 8.0$, 1.6 Hz, 1H), 7.47 (dt, $J = 8.8$, 2 Hz, 1H), 7.41–7.30 (m, 6H), 6.94 (dt, $J = 8.4$, 0.8 Hz, 1H), 6.69 (d, $J = 8.8$ Hz, 1H), 5.53 (dd, $J = 10.0$, 8.4 Hz, 1H), 4.75 (dd, $J = 10.0$, 8.4 Hz, 1H), 4.17 (t, $J = 8.4$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 165.2$, 153.5, 145.7, 142.5, 142.1, 137.1, 132.6, 129.7, 128.8, 127.7, 126.4, 122.4, 119.5, 117.5, 113.7, 111.5, 73.3, 69.9 ppm; HRMS (ESI): *m/z* calcd for $C_{20}H_{17}ClN_3O$ ([M + H]$^+$) 350.1055, found 350.1054; $[\alpha]_D^{20} = +334.13°$ cm^2 g^{-1} ($c = 0.55$, CH_2Cl_2).

2-[4-Fluoro-2-[(4*S*)-4-phenyl-4,5-dihydrooxazol-2-yl]-phenylamino]-5-nitropyridine (4c, $C_{20}H_{15}FN_4O_3$) Ligand **4c** was obtained from 154 mg **8c** and 102 mg 2-bromo-5-nitropyridine (**9c**) after 20 h of reflux. It was purified by column chromatography (CH_2Cl_2/hexanes 5:3.5) and recrystallized from ethanol. Yellow crystals; yield 66 mg (35%); m.p.: 161–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 12.34$ (s, 1H), 9.16 (d, $J = 2.4$ Hz, 1H), 9.01 (dd, $J = 9.2$, 5.2 Hz, 1H), 8.19 (dd, $J = 8.8$, 2.4 Hz, 1H), 7.67 (dd, $J = 8.8$, 2.8 Hz, 1H), 7.4–7.30 (m, 6H), 6.65 (d, $J = 9.2$ Hz, 1H), 5.56 (dd, $J = 10.0$, 8.4 Hz, 1H), 4.81 (dd, $J = 10.0$, 8.4 Hz, 1H), 4.24 (t, $J = 8.4$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.3$ (d, $J = 2.5$ Hz, C=N), 158.2, 157.3 (d, $J_{C,F} = 240.9$ Hz, C-F), 145.8, 141.4, 137.3 (d, $J_{C,F} = 2.5$ Hz, C–NH in Ph ring), 137.2, 132.2, 129.0, 128.0, 126.3, 121.0 (d, $J_{C,F} = 7.1$ MHz, C_{meta}–CF), 119.6 (d, $J_{C,F} = 21.8$ Hz, C_{ortho}–CF), 115.8 (d, $J_{C,F} = 24.6$ Hz, C_{ortho}–CF), 113.9 (d, $J_{C,F} = 7.6$ Hz, C_{meta}–CF), 111.6, 73.6, 70.0 ppm; HRMS (ESI): *m/z* calcd for $C_{20}H_{16}FN_4O_3$ ([M + H]$^+$) 379.3708, found 379.3706; $[\alpha]_D^{20} = +458.35°$ cm^2 g^{-1} ($c = 0.66$, CH_2Cl_2).

3-Chloro-5-nitro-2-[2-[(4*S*)-4-phenyl-4,5-dihydrooxazol-2-yl]-phenylamino]pyridine (4d, $C_{20}H_{15}ClN_4O_3$) Ligand **4d** was obtained from 143 mg **8a** and 119 mg 2,3-dichloro-5-nitropyridine (**9e**) after 20 h of reflux. It was purified by column chromatography (CH_2Cl_2/hexanes 5:3.5) and recrystallized from ethanol. Yellow crystals; yield 130 mg (66%); m.p.: 157–159 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 12.87$ (s, 1H), 9.10–9.08 (m, 2H), 8.31 (d, $J = 2.4$ Hz, 1H), 8.00 (dd, $J = 8.0$, 2.0 Hz, 1H), 7.57 (dt, $J = 8.8$, 2.2 Hz, 1H), 7.40–7.32 (m, 5H), 7.17 (dt, $J = 8.0$, 2.0 Hz, 1H), 5.57 (dd, $J = 10.0$, 8.8 Hz, 1H), 4.81 (dd, $J = 10.0$, 8.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.4$, 154.8, 142.8, 141.5, 140.1, 136.6, 132.5, 131.5, 129.6, 128.8, 127.8, 126.5, 122.4, 119.6, 117.6, 113.8, 73.4, 69.9 ppm; HRMS (ESI): *m/z* calcd for $C_{20}H_{16}ClN_4O_3$ ([M + H]$^+$) 395.0905, found 395.0909; $[\alpha]_D^{20} = +412.80°$ cm^2 g^{-1} ($c = 0.5$, CH_2Cl_2).

6-Bromo-2-[2-[(4*S*)-4-phenyl-4,5-dihydrooxazol-2-yl]-phenylamino]pyridine (4e, $C_{20}H_{16}BrN_3O$) Ligand **4e** was obtained from 119 mg **8a** (0.5 mmol) and 260 mg 2,6-dibromopyridine (**9d**, 1.1 mmol) after 20 h of reflux. It was purified by column chromatography (CH_2Cl_2/hexanes 1:1) and recrystallized from ethanol. White crystals; yield 163 mg (83%); m.p.: 139 -141 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 11.89$ (s, 1H), 8.79 (dd, $J = 8.4$, 0.h Hz, 1H), 7.92 (dd, $J = 8.4$, 2.0 Hz, 1H). 7.52 (dt, $J = 8.4$, 1.6 Hz, 1H), 7.40–7.28 (m, 7H), 6.98 (dt, $J = 8.4$, 1.2 Hz, 1H), 6.92 (d, 7.6 Hz, 1H), 6.64 (d, $J = 8.0$ Hz, 1H), 5.53 (dd, $J = 10.0$, 8.4 Hz, 1H), 4.75 (dd, $J = 9.6$, 8.0 Hz, 1H), 4.18 (t, $J = 8.0$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 165.3$, 154.9, 142.2, 139.4, 139.0, 132.8, 129.6, 128.8, 127.9, 127.7, 126.4, 119.7, 118.5, 117.6, 111.5, 110.973.2, 69.9 ppm; HRMS (ESI): *m/z* calcd for $C_{20}H_{16}BrN_3O$ ([M + H]$^+$) 394.0550 and 396.0529, found 394.0551 and 396.0530; $[\alpha]_D^{20} = +183.64°$ cm^2 g^{-1} ($c = 1.1$, CH_2Cl_2).

5-Nitro-2-[2-[(4*S*)-4-*tert*-butyl-4,5-dihydrooxazol-2-yl]-phenylamino]pyridine (4f, $C_{18}H_{20}N_4O_3$) Ligand **4f** was obtained from 131 mg **8b** and 101.5 mg 2-bromo-5-nitropyridine (**9c**) after 20 h of reflux. It was purified by column chromatography (CH_2Cl_2/hexanes 5:3.5) and recrystallized from ethanol. Yellow crystals; yield 24 mg (14%); m.p.: 141–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 12.73$ (s, 1H), 9.17 (d, $J = 2.4$ Hz, 1H), 8.95 (d, $J = 8.0$ Hz, 1H), 8.25 (dd, $J = 9.2$, 2.8 Hz, 1H), 7.88 (dd, $J = 8.0$, 1.6 Hz, 1H), 7.51 (dt, $J = 8.8$, 1.6 Hz, 1H), 7.06 (dt, $J = 8.4$, 1.2 Hz, 1H), 6.72 (d, $J = 9.2$ Hz, 1H), 4.38–4.32 (m, 1H), 4.23–4.20 (m, 1H), 1.00 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 163.8$, 158.5, 146.0, 140.8, 137.1, 132.4, 132.2, 129.4, 121.4, 119.0, 112.9, 111.5, 76.0, 67.4, 33.9, 25.9 ppm; HRMS (ESI): *m/z* calcd for $C_{18}H_{21}N_4O_3$ ([M + H]$^+$) 341.1608, found 341.1609; $[\alpha]_D^{20} = +67.91°$ cm^2 g^{-1} ($c = 1.1$, CH_2Cl_2).

6-Bromo-2-[2-[(3a*R*,8a*S*)-8,8a-dihydro-3a*H*-indeno[1,2-*d*]-oxazol-2-yl]phenyl]aminopyridine (4g, $C_{21}H_{16}BrN_3O$) Ligand **4g** was obtained from 125 mg **8g** (0.5 mmol) and 260 mg 2,6-dibromopyridine (**9d**, 1.1 mmol) after 20 h of reflux. After evaporation of solvent the mixture was subjected to column chromatography (CH_2Cl_2/hexanes 5:3.5) after which the product was isolated as a mixture with unreacted 2,6-dibromopyridine. The residue of 2,6-dibromopyridine was removed by sublimation.

Chemically pure ligand **4g** was recrystallized from ethanol. Yellow crystals; yield 175 mg (86%); m.p.: 166–169 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 11.77$ (s, 1H), 8.68 (dd, $J = 8.4$, 0.4 Hz, 1H), 7.83 (dd, $J = 7.6$, 1.2 Hz, 1H), 7.53–7.51 (m, 1H), 7.47–7.33 (m, 3H), 7.30–7.24 (m, 2H), 6.94–6.88 (m, 2H), 6.76 (d, $J = 8.0$ Hz, 1H), 5.83 (d, $J = 8.0$ Hz, 1H), 5.43 (appt, $J = 2.0$ Hz, 1H), 3.54–3.42 (m, 1H), 3.41–3.35 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.2$, 155.0, 141.8, 140.1, 139.7, 139.0, 132.5, 129.4, 128.6, 127.5, 127.0, 125.4, 125.2, 119.6, 118.4, 117.5, 111.8, 110.7, 81.5, 39.6 ppm, signal of one aliphatic carbon atom overlaps with the solvent signal; HRMS (ESI): *m/z* calcd for $C_{21}H_{17}BrN_3O$ ($[M+H]^+$) 406.0549 and 408.0529, found 406.0555 and 408.0532; $[\alpha]_D^{20} = -227.2°$ cm^2 g^{-1} ($c = 0.53$, CH_2Cl_2).

2-[2-[(3a*R*,8a*S*)-8,8a-Dihydro-3a*H*-indeno[1,2-*d*]oxazol-2-yl]-4-fluorophenyl]amino-5-fluoropyridine (4h, $C_{21}H_{15}F_2N_3O$) Ligand **4h** was obtained from 161 mg **8h** and 88 mg 2-bromo-5-fluoropyridine (**9a**) after 20 h of reflux. It was purified by column chromatography (CH_2Cl_2/hexanes 5:3.5) and recrystallized from ethanol. White crystals; yield 44 mg (24%); m.p.: 225–226 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 11.40$ (s, 1H), 8.65 (dd, $J = 9.2$, 5.2 Hz, 1H), 8.10 (d, $J = 3.2$ Hz, 1H), 7.54–7.51 (m, 2H), 7.34–7.28 (m, 4H), 7.14–7.09 (m, 1H), 6.79 (dd, $J = 9.2$, 3.6 Hz, 1H), 5.85 (d, $J = 8.0$ Hz, 1H), 5.43 (appt, $J = 8.0$ Hz, 1H), 3.56–3.64 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 163.5$, 155.5 (d, $J_{C,F} = 237.0$ Hz, C-F in Ph ring), 154.4 (d, $J_{C,F} = 245.0$ Hz, C-F in pyridine ring), 151.6, 141.6, 139.6, 139.0, 133.8 (d, $J_{C,F} = 24.4$ Hz, C_{ortho}–CF in pyridine ring), 128.7, 127.6, 125.5, 125.3 (d, $J_{C,F} = 20.4$ Hz, C_{ortho}–CF in pyridine ring), 125.2, 119.2 (d, $J_{C,F} = 21.7$ Hz, C_{ortho}–CF in Ph ring), 118.5 (d, $J_{C,F} = 6.7$ Hz, C_{meta}–CF in Ph ring), 115.5 (d, $J_{C,F} = 24.4$ Hz, C_{ortho}–CF in Ph ring), 113.1 (d, $J_{C,F} = 3.9$ Hz, C_{meta}–CF in pyridine ring), 112.2 (d, $J_{C,F} = 6.9$ Hz, C_{meta}–CF in Ph ring), 81.8, 76.8, 39.6 ppm; HRMS (ESI): *m/z* calcd for $C_{21}H_{16}F_2N_3O$ ($[M+H]^+$) 364.1253, found 364.1256; $[\alpha]_D^{20} = -361.9°$ cm^2 g^{-1} ($c = 0.53$, CH_2Cl_2).

3-[4-Fluoro-2-[(4*S*)-4-phenyl-4,5-dihydrooxazol-2-yl]phenylamino]-5-phenyl-1,2,4-triazine (5a, $C_{24}H_{18}FN_5O$) Ligand **5a** was obtained from 154 mg **8c** and 118 mg 3-bromo-5-phenyl-1,2,4-triazine (**10**) after 3 h of reflux. It was purified by column chromatography (hexanes/AcOEt 5:1) and recrystallized from ethanol. Yellow crystals; yield 138 mg (67%); m.p.: 155–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 12.48$ (s, 1H), 9.23 (s, 1H), 9.01 (dd, $J = 9.6$, 5.2 Hz, 1H), 8.14–8.12 (m, 2H), 7.69 (dd, $J = 9.6$, 3.2 Hz, 1H), 7.59–7.54 (m, 3H), 7.40–7.38 (m, 4H), 7.34–7.27 (m, 2H), 5.67 (dd, $J = 10.4$, 8.8 Hz, 1H), 4.84 (dd, $J = 10.4$, 8.4 Hz, 1H), 4.28 (appt, $J = 8.4$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 163.8$, 160.3, 156.7 (d, $J_{C,F} = 239.7$ Hz, C-F), 155.6, 141.7, 139.3, 137.1 (d, $J_{C,F} = 2.2$ Hz, C–NH in Ph ring), 133.8, 132.2, 1292, 128.8, 127.7, 127.5, 126.4, 120.9 (d, $J_{C,F} = 7.1$ Hz, C_{meta}–CF), 119.4 (d, $J_{C,F} = 21.8$ Hz, C_{ortho}–CF), 115.8 (d, $J_{C,F} = 24.6$ Hz, C_{ortho}–CF), 114.1 (d, $J_{C,F} = 7.6$ Hz, C_{meta}–CF), 73.4, 70.0 ppm; HRMS (ESI): *m/z* calcd for $C_{24}H_{19}FN_5O$ ($[M+H]^+$) 412.1568, found 412.1565; $[\alpha]_D^{20} = +295.56°$ cm^2 g^{-1} ($c = 0.51$, CH_2Cl_2).

3-[4-Fluoro-2-[(4*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl]phenylamino]-5-phenyl-1,2,4-triazine (5b, $C_{21}H_{20}FN_5O$) Ligand **5b** was obtained from 133 mg **8d** and 118 mg 3-bromo-5-phenyl-1,2,4-triazine (**10**) after 3 h of reflux. It was purified by column chromatography (hexanes/AcOEt 10:1) and recrystallized from ethanol. Yellow crystals; yield 113 mg (60%); m.p.: 148–149 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 12.68$ (s, 1H), 9.23 (s, 1H), 9.01 (dd, $J = 9.2$, 5.2 Hz, 1H), 8.18–8.16 (m, 2H), 7.62–7.55 (m, 4H), 7.25 (ddd, $J = 9.6$, 8.0, 3.2 Hz, 1H), 4.46 (dd, $J = 9.2$, 8.0 Hz, 1H), 4.28–4.22 (m, 1H), 4.11 (appt, $J = 8.0$ Hz, 1H), 1.98–1.82 (m, 1H); 1.19 (d, $J = 6.8$ Hz, 3H), 1.05 (d, $J = 6.8$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 162.4$ (d, $J = 2.5$ Hz, C=N), 160.1, 156.5 (d, $J_{C,F} = 239.4$ Hz, C-F), 155.5, 139.1, 137.0 (d, $J = 2.3$ Hz, C–NH in Ph ring), 133.8, 132.1, 129.1, 127.4, 120.6 (d, $J_{C,F} = 7.0$ Hz, C_{meta}–CF), 119.0 (d, $J_{C,F} = 21.8$ Hz, C_{ortho}–CF), 115.5 (d, $J_{C,F} = 24.5$ Hz, C_{ortho}–CF), 114.0 (d, $J_{C,F} = 7.7$ Hz, C_{meta}–CF), 73.0, 69.8, 33.5, 19.0, 18.9 ppm; HRMS (ESI): *m/z* calcd for $C_{21}H_{21}FN_5O$ ($[M+H]^+$) 378.1725, found 378.1721; $[\alpha]_D^{20} = +19.03°$ cm^2 g^{-1} ($c = 0.51$, CH_2Cl_2).

3-[4-Fluoro-2-[(4*S*)-4-*tert*-butyl-4,5-dihydrooxazol-2-yl]phenylamino]-5-phenyl-1,2,4-triazine (5c, $C_{22}H_{22}FN_5O$ Ligand **5c** was obtained from 142 mg **8e** and 118 mg 3-bromo-5-phenyl-1,2,4-triazine (**10**) after 3.5 h of reflux. It was purified by column chromatography (hexanes/AcOEt 5:1) and recrystallized from ethanol. Yellow crystals; yield 78 mg (40%); m.p.: 162–164 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 12.73$ (s, 1H), 9.24 (s,1H), 9.03 (dd, $J = 9.6$, 5.2 Hz, 1H), 8.18–8.16 (m, 2H), 7.61–7.53 (m, 4H), 7.28–7.23 (m, 1H), 4.40–4.38 (m, 1H), 4.30–4.20 (m, 2H), 1.06 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 162.4$ (d, $J = 2.5$ Hz, C=N), 160.0, 156.4 (d, $J_{C,F} = 239.3$ Hz, C-F), 155.4, 139.0, 137.0 (d, $J_{C,F} = 2.2$ Hz, C–NH in Ph ring), 133.7, 132.1, 129.1, 127.3, 120.6 (d, $J_{C,F} = 7.1$ Hz, C_{meta}–CF), 119.0 (d, $J_{C,F} = 21.8$ Hz, C_{ortho}–CF), 115.4 (d, $J_{C,F} = 24.6$ Hz, C_{ortho}–CF), 113.8 (d, $J_{C,F} = 7.6$ Hz, C_{meta}–CF), 76.2, 67.6, 34.0, 25.8 ppm; HRMS (ESI): *m/z* calcd for $C_{22}H_{23}FN_5O$ ($[M+H]^+$) 392.1881, found 392.1877; $[\alpha]_D^{20} = +19.29°$ cm^2 g^{-1} ($c = 0.57$, CH_2Cl_2).

3-[4-Nitro-2-[(4*S*)-4-phenyl-4,5-dihydrooxazol-2-yl]phenylamino]-5-phenyl-1,2,4-triazine (5d,

$C_{24}H_{18}N_6O_3$) Ligand **5d** was obtained from 170 mg **8f** and 118 mg 3-bromo-5-phenyl-1,2,4-triazine (**10**) after 20 h of reflux. It was purified by column chromatography (CH_2Cl_2/hexanes 8:1) and recrystallized from ethanol. Yellow crystals; yield 140 mg (64%); m.p.: 218–220 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 13.17$ (s, 1H), 9.36 (s, 1H), 9.25 (d, $J = 9.6$ Hz, 1H), 8.91 (d, $J = 3.2$ Hz, 1H), 8.43 (dd, $J = 2.8$, 9.6 Hz, 1H), 8.17–8.14 (m, 2H), 7.63–7.55 (m, 3H), 7.41–7.40 (m, 4H), 7.36–7.34 (m, 1H), 5.70 (dd, $J = 10.4$, 8.8 Hz, 1H), 4.91 (dd, $J = 10.4$, 8.8 Hz, 1H), 4.36 (t, $J = 8.4$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.5$, 160.4, 155.4, 142.2, 141.2, 140.7, 138.1, 133.7, 132.5, 132.2, 129.7, 129.3, 128.9, 127.8, 127.6, 126.4, 119. 2, 113.9, 73.3, 70.5 ppm; HRMS (ESI): *m/z* calcd for $C_{24}H_{19}N_6O_3$ ($[M+H]^+$) 439.1513, found 439.1510; $[\alpha]_D^{20} = +217.46°$ cm^2 g^{-1} ($c = 1.0$, CH_2Cl_2).

General procedure for the catalytic enantioselective Henry reaction

A mixture of 5 mg $Cu(OAc)_2 \cdot H_2O$ (0.025 mmol, 5 mol%) and ligand **4a**-**4h** or **5a**-**5d** (0.025 mmol, 5 mol %) in 2 cm^3 anhydrous 2-propanol was stirred at room temperature for 4 h under argon atmosphere to obtain copper complex. The aldehyde **11a**-**11i** (0.5 mmol) and 270 cm^3 nitromethane (**12**) were added and the reaction was conducted at room temperature for 4 days. Then the solvent was removed under reduced pressure and the product **13a**-**13i** was isolated by column chromatography. The ee values of the nitro-alcohols were determined by chiral HPLC analysis using Chiracel OD-H column. The absolute configurations of the products were assigned by comparing their specific rotations or the retention times in HPLC with literature data [24–27]. ^{1}H NMR and ^{13}C NMR spectra of the nitro-alcohols were found to be with agreement with the ones described in literature [24–27]. Below are presented data for nitro-alcohols obtained in reactions conducted in the presence of ligand **5a**.

(*S*)-2-Nitro-1-(4-nitrophenyl)ethanol (13a) Compound **13a** was obtained according to the general procedure and purified by column chromatography (hexanes:ethyl acetate 5:1). White solid; yield 73 mg (69%); $[\alpha]_D^{20} = +15.4°$ cm^2 g^{-1} ($c = 1.23$, CH_2Cl_2); HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 85:15, flow rate: 1.0 cm^3/min, $\lambda = 215$ nm), $t_{minor} = 13.2$, $t_{major} = 16.4$, 34% ee. ^{1}H NMR and ^{13}C NMR spectra were found to be with agreement with the ones described in Ref. [27].

(*S*)-1-(2-Bromophenyl)-2-nitroethanol (13b) Compound **13b** was obtained according to the general procedure and purified by column chromatography (hexanes:ethyl acetate 8:1). Colorless oil; yield 109 mg (89%); $[\alpha]_D^{20} = +33.6°$ cm^2 g^{-1} ($c = 1.09$, CH_2Cl_2); HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 96:4, flow rate: 0.5 cm^3/min, $\lambda = 215$ nm), $t_{minor} = 23.1$, $t_{major} = 25.5$, 64% ee. ^{1}H NMR and ^{13}C NMR spectra were found to be with agreement with the ones described in Ref. [25].

(*S*)-2-Nitro-1-(3-nitrophenyl)ethanol (13c) Compound **13c** was obtained according to the general procedure and purified by column chromatography (hexanes:ethyl acetate 2.5:1). Colorless solid; yield 85 mg (80%); $[\alpha]_D^{20} = +18.3°$ cm^2 g^{-1} ($c = 1.05$, CH_2Cl_2); HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 90:10, flow rate: 1.0 cm^3/min, $\lambda = 215$ nm), $t_{minor} = 19.9.2$, $t_{major} = 22.7$, 42% ee. ^{1}H NMR and ^{13}C NMR spectra were found to be with agreement with the ones described in Ref. [25].

(*S*)-2-Nitro-1-(2-nitrophenyl)ethanol (13d) Compound **13d** was obtained according to the general procedure and purified by column chromatography (hexanes:ethyl acetate 5:1). Brown solid; yield 77 mg (73%); $[\alpha]_D^{20} = -18.3°$ cm^2 g^{-1} ($c = 1.07$, CH_2Cl_2); HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 90:10, flow rate: 1.0 cm^3/min, $\lambda = 215$ nm), $t_{minor} = 11.6$, $t_{major} = 12.8$, 66% ee. ^{1}H NMR and ^{13}C NMR spectra were found to be with agreement with the ones described in Ref. [27].

(*S*)-1-(4-Chlorophenyl)-2-nitroethanol (13e) Compound **13e** was obtained according to the general procedure and purified by column chromatography (hexanes:ethyl acetate 7:1). Colorless oil; yield 56 mg (53%); $[\alpha]_D^{20} = +27.8°$ cm^2 g^{-1} ($c = 1.08$, CH_2Cl_2); HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 90:10, flow rate: 0.5 cm^3/min, $\lambda = 215$ nm), $t_{minor} = 27.9$, $t_{major} = 35.0$, 55% ee. ^{1}H NMR and ^{13}C NMR spectra were found to be with agreement with the ones described in Ref. [27].

(*S*)-1-(3-Chlorophenyl)-2-nitroethanol (13f) Compound **13f** was obtained according to the general procedure and purified by column chromatography (hexanes:ethyl acetate 7:1). Colorless oil; yield 17 mg (17%); $[\alpha]_D^{20} = +22.8°$ cm^2 g^{-1} ($c = 0.92$, CH_2Cl_2); HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 90:10, flow rate: 1.0 cm^3/min, $\lambda = 215$ nm), $t_{minor} = 10.5$, $t_{major} = 12.6$, 45% ee. ^{1}H NMR and ^{13}C NMR spectra were found to be with agreement with the ones described in Ref. [25].

(*S*)-1-(2-Chlorophenyl)-2-nitroethanol (13g) Compound **13g** was obtained according to the general procedure and purified by column chromatography (hexanes:ethyl acetate 7:1). Colorless oil; yield 97 mg (96%); $[\alpha]_D^{20} = +42.2°$ cm^2 g^{-1} ($c = 1.2$, CH_2Cl_2); HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 98:2, flow rate: 1.0 cm^3/min, $\lambda = 215$ nm), $t_{minor} = 25.0$, $t_{major} = 29.1$, 87% ee. ^{1}H NMR and ^{13}C NMR

spectra were found to be with agreement with the ones described in Ref. [26].

(*S*)-1-(2-Methoxyphenyl)-2-nitroethanol (13h) Compound **13h** was obtained according to the general procedure and purified by column chromatography (hexanes:ethyl acetate 10:1). Yellow oil; yield 82 mg (83%); $[\alpha]_D^{20} = +34.5°$ cm^2 g^{-1} ($c = 1.1$, CH_2Cl_2); HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 90:10, flow rate: 1.0 cm^3/min, $\lambda = 215$ nm), $t_{minor} = 8.7$, $t_{major} = 9.8$, 62% ee. ^{1}H NMR and ^{13}C NMR spectra were found to be with agreement with the ones described in Ref. [27].

(*S*)-1-(1-Naphthyl)-2-nitroethanol (13i) Compound **13i** was obtained according to the general procedure and purified by column chromatography (hexanes:ethyl acetate 10:1). Yellow oil; yield 40 mg (37%); $[\alpha]_D^{20} = +15.9°$ cm^2 g^{-1} ($c = 1.1$, CH_2Cl_2); HPLC (Chiralcel OD-H, hexane/*i*-PrOH = 90:10, flow rate: 1.0 cm^3/min, $\lambda = 215$ nm), $t_{minor} = 13.9$, $t_{major} = 18.2$, 39% ee. ^{1}H NMR and ^{13}C NMR spectra were found to be with agreement with the ones described in Ref. [25].

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