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Structural characterization of copper complexes with chiral 1,2,4-triazine-oxazoline ligands

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Abstract: The crystal structure determination of oxazoline-1,2,4-triazine ligand **1f** and pyridine-oxazoline ligand **2g** was used to analyze their conformational preferences when forming complexes with metals. Proton nuclear magnetic resonance (^{1}H NMR), electrospray ionization mass spectrometry and UV-vis spectroscopy as well as theoretical calculation using molecular mechanics (MM) were adopted to study the composition and geometry of oxazoline-1,2,4-triazine ligands **1** complexes with copper(II) acetate monohydrate. The study revealed that during the complexation, (i) Cu(II) ion is reduced to Cu(I) upon the ligand-to-metal charge transfer transition and (ii) the ligands form with copper(I) 2:1 (L:Cu) complexes of tetrahedral geometry. On the basis of the findings, the catalytic cycle and the active transition state for the enantioselective nitroaldol reaction (the Henry reaction) catalyzed by **1**–Cu are proposed.

Keywords: asymmetric catalysis; chiral 1,2,4-triazine-oxazoline ligands; enantioselective nitroaldol reaction; X-ray diffraction analysis.

Introduction

Compounds that contain the oxazoline ring have been called privileged ligands for asymmetric catalysis because of their ability to catalyze various enantioselective processes with high enantioselectivity [1, 2]. We have previously reported the synthesis and asymmetric activity of chiral oxazoline ligands of classes **1** [3–5], **2** [5] and **3** [6] (Figure 1). Ligands of class **1** contain in their structure oxazoline and 1,2,4-triazine rings linked by the N-phenylamine unit. These ligands vary in the type of substituent in the oxazoline ring and substitution pattern in the 1,2,4-triazine ring. The enantiocontrolling abilities of the ligands have been assessed in the asymmetric nitroaldol reaction of a series of aromatic and aliphatic aldehydes which provide the β-nitro alcohols with optical purity of up to 92% and chemical yields up to 95%. It has been shown that the enantioselectivity of the nitroaldol reaction is controlled by the substituent on the oxazoline ring, while the chemical yield depends on the substituents in 1,2,4-triazine ring. The ligands with 1,2,4-triazine rings possessing a phenyl substituent in the C-5 position and unsubstituted at C-6 appear the most promising in the asymmetric nitroaldol reaction. Among them the ligand **1f** with a phenyl substituent in the oxazoline ring and ligand **1n** with a fused indane moiety exhibit the highest activity. Ligand **1p** with two stereocenters catalyzes the nitroaldol reaction with enantioselectivity comparable to that obtained by using ligand **1f** possessing one stereocenter in the oxazoline ring. This indicates that an additional stereocenter at the C-5 position of the oxazoline ring in ligands **1n**, **1o** and **1p** does not have any influence on the stereochemistry of the Henry reaction.

Ligands of type **2** can be considered as analogues of ligands of type **1** in which the 1,2,4-triazine ring is replaced by a pyridine, pyrimidine or pyrazine ring. They are much less active in the enantioselective Henry reaction in comparison to ligands **1**. The use of ligands **2a**–**2d** in the nitroaldol reaction allows β-nitro alcohols to be obtained with optical purity not exceeding 34% and chemical yield varying within the range of 10%–80%. Among ligands **2**, the highest enantioselectivities have been achieved with ligands **2g** and **2h** for the reactions of *ortho*-substituted benzaldehydes. The β-nitro alcohols are formed with enantiopurity of 63%–67%, but with low chemical yields of 22%–44% [5]. The results obtained for ligands **2** indicate that the presence of a 1,2,4-triazine ring in the ligand structure is essential in promoting high yields and enantioselection. This statement is further confirmed by the results received in reactions conducted in the presence of ligands **4a** and **4b** (Figure 2) in which the 1,2,4-triazine ring is replaced by phenyl rings. Very low enantioselection, not exceeding 33% and yield up to 44%, has been observed in these reactions [3].

Changing the *N*-phenylamine unit in ligands **1** to pyridine-2-amine or 2-aminopyridine 1-oxide causes the total

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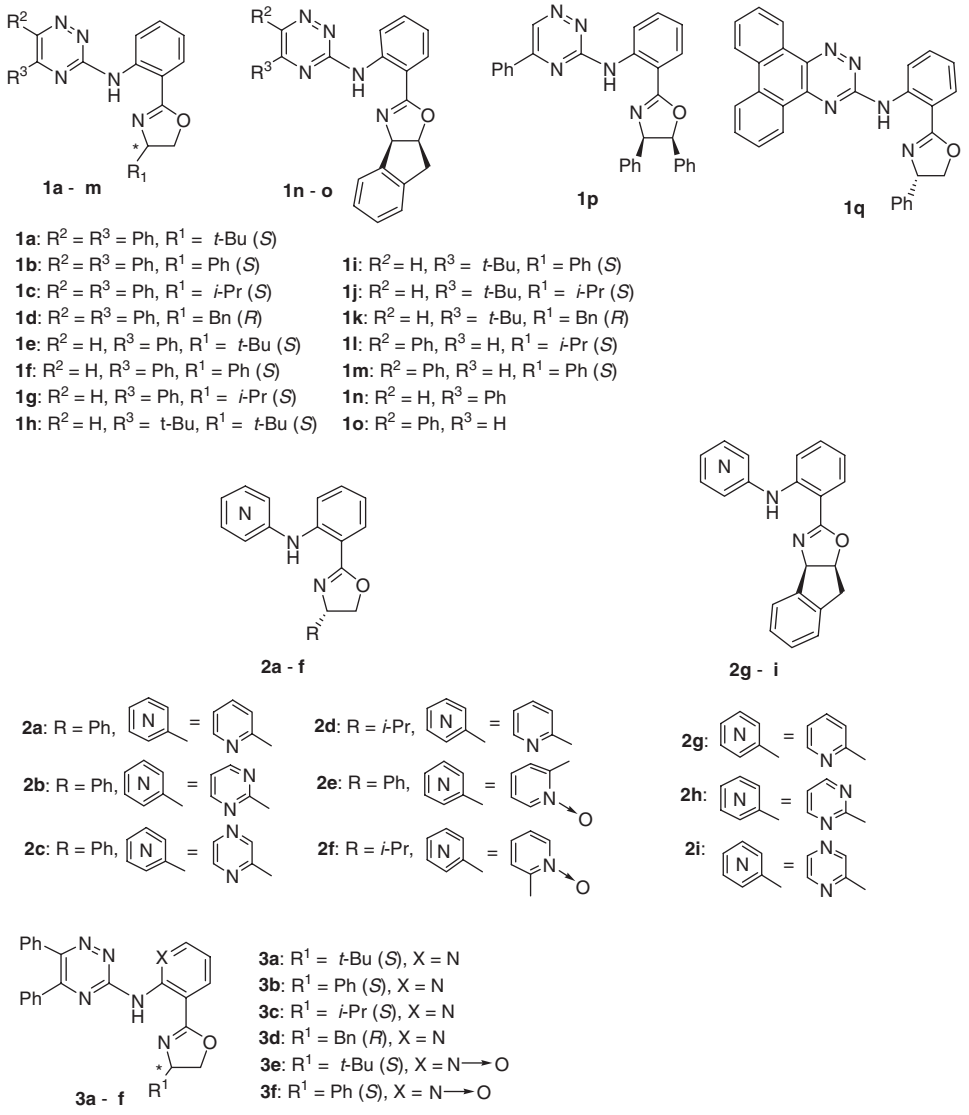


Figure 1 Chiral oxazoline ligands of the types **1, 2** and **3.**

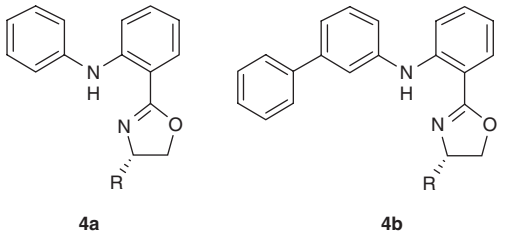


Figure 2 Ligands **4a** and **4b,** R = Ph.

loss of the stereocontrolling ability of the resultant ligands **3**. The nitroaldol reactions catalyzed by complexes **3**–Cu produce racemic products, however, with relatively good yields of up to 79% [6]. A different mode of copper complexation by ligands **3** in comparison to ligands **1** has been postulated. The nitrogen atom of the oxazoline ring in **3** probably does not participate in the copper ion complexation as lack of enantioselection is observed.

In this work, catalytically active complexes for the nitroaldol reaction were prepared *in situ* by mixing ligands **1, 2**, or **3** and $Cu(OAc)_2 \cdot H_2O$ in 2-propanol or a mixture of 2-propanol/tetrahydrofuran (THF) prior to addition of substrates. Efforts toward obtaining a crystal of complex appropriate for X-ray diffraction analysis were unsuccessful. As the isolation of complexes thus formed was not possible, intensive efforts were made to establish the preferential stoichiometry and geometry of complexes and, as a consequence, to understand the stereoinduction mechanism. The crystal structure determination of ligands **1f** and **2g**, UV-vis, nuclear magnetic resonance (NMR) and electrospray ionization high resolution mass spectroscopy (ESI-HR-MS) studies of the *in situ* formed complexes as

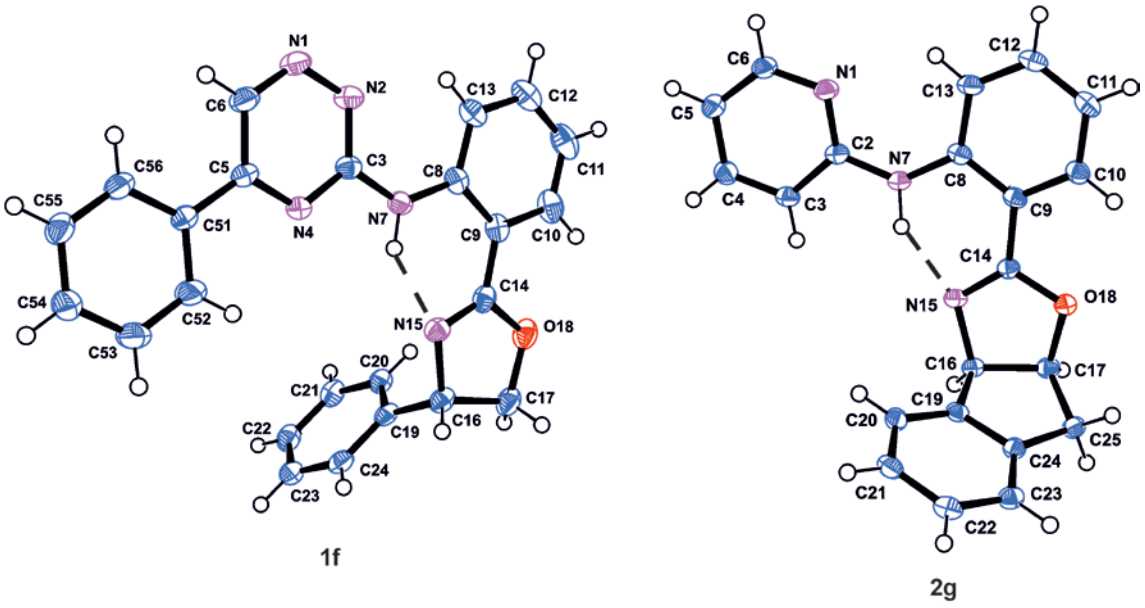


Figure 3 A view of the X-ray molecular structures of **1f** and **2g** with the atomic labeling and 50% probability displacement ellipsoids for non-H atoms.

well as theoretical calculation using molecular mechanics (MM) method were adopted in the research. In this paper, we present the results of the work.

Results and discussion

In order to confirm the assumed molecular structures of investigated ligands and to predict their coordination abilities, the X-ray diffraction analysis of **1f** and **2g** as model compounds was performed. The structure and conformation of the molecules **1f** and **2g** in the crystal are shown in Figure 3.

The X-ray diffraction investigations confirmed the previously assumed absolute configuration *S* at C16 atom for **1f**, and *R* at C16 and *S* at C17 atoms for **2g**. The bond lengths and angles in molecules of **1f** and **2g** do not differ significantly from those reported for similar structure of *N*-{2-[(4*S*)-4-tert-butyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl}-5,6-diphenyl-1,2,4-triazin-3-amine [7]. In both molecules, the central secondary N7-amino group is planar with the sum of the angles around the N-atom of 360.6° in **1f** and 359.8° in **2g**, and it is co-planar with the triazine (**1f**) and pyridine (**2g**) rings and oxazolylphenyl moiety with the torsion angles N2(N1)–C3(C2)–N7–C8 of 1.6(4)° and 1.0(3)°, the torsion angles C3(C2)–N7–C8–C9 of 2.2(5)° and –7.5(4)° and the torsion angles C8–C9–C14–C15 of –2.5(5)° and –3.1(3)° for **1f** and **2g**, respectively. This planarity is stabilized by the intramolecular hydrogen bonds N7–H7…N15, C10–H10…O18 and C13–H13…N2(N1) in **1f** and **2g**, and additionally C52–H52…N4 in **1f** (Table 1).

Moreover, the phenyl ring C19…C24 adopts a similar *gauche* conformation with respect to oxazoline ring in both molecules with the torsion angles N15–C16–C19–C20 of 63.0(3)° in **1f** and 52.5(3)° in **2g**, but this conformation is frozen in the indeno[(1,2-*d*)(1,3)oxazol-2-yl]phenyl tricyclic system of **2g**. The partially saturated five-membered oxazoline and cyclopentene rings are slightly distorted from planarity with the maximum deviation from the mean plane of 0.083(3) Å and 0.114(3) Å for the oxazoline ring in **1f** and **2g**, respectively, and 0.107(2) Å for cyclopentene ring in **2g**.

The presence of intramolecular N7–H7…N15 hydrogen bond in **1f** and **2g** determines the geometry of molecule, in which the chelation of a metal is possible between

Table 1 Intramolecular hydrogen-bond geometry (Å, °) in compounds **1f** and **2g**.

D–H…A	D–H	H…A	D…A	D–H…A
1f				
N7–H7…N15	0.90(4)	1.99(4)	2.737(3)	140(3)
C10–H10…O18	0.93	2.33	2.699(4)	103
C13–H13…N2	0.93	2.21	2.845(4)	125
C52–H52…N4	0.93	2.49	2.807(4)	100
2g				
N7–H7…N15	0.94(3)	1.84(3)	2.665(2)	146(3)
C10–H10…O18	0.93	2.40	2.752(3)	103
C13–H13…N1	0.93	2.33	2.944(3)	123

N7-amine and N15-oxazoline atoms. This kind of chelation of the zinc atom is observed in the complex of *N*-{2-[(4*S*)-4-*tert*-butyl-4,5-dihydro-1,3-oxazol-2-yl]phenyl}pyridine-2-amine and $ZnCl_2$ with the change of the position of the pyridine ring on the opposite with respect to the amine group and shift of the H7 proton to the pyridyl nitrogen atom [8]. Moreover, in the conformation observed in the crystal of **1f**, an additional (or competitive with the N7-amine atom) coordination center at the N4-triazine atom is possible. On the one hand, this atom can accept a proton from the amino group without changing the position of the triazine ring or, on the other hand, it can become an additional coordination center for the metal with proton transfer from the amino group to the nitrogen N2 atom of the triazine ring. The N4 and N2 nitrogen atoms of the triazine ring are recognized as being better proton acceptors than the N1 nitrogen atom [9].

Proton nuclear magnetic resonance (^{1}H NMR) analysis of the mixtures obtained after mixing ligand with $Cu(OAc)_2{\cdot}H_2O$ revealed the presence of two sets of signals in the spectra: signals of free ligand protons and signals shifted toward lower field attributed to proton of the complex. Figure 4 presents spectra of ligand **1f** and **1f**–Cu complex obtained after mixing ligand **1f** and $Cu(OAc)_2{\cdot}H_2O$. In the spectra of **1f**–Cu, diagnostic signals of the free-ligand oxazoline-ring protons are present at 4.26, 4.83 and 5.66 ppm. The signals at 5.95, 6.52 and 6.70 ppm are attributed to the respective oxazoline protons of complex **1f**–Cu.

The shift toward the lower field must be a result of deshielding caused by transferring the electron pair from the oxazoline nitrogen to the copper ion. That shifting is not observed in the spectra of **3a**–Cu. Signals from the oxazoline protons of **3a**–Cu complex and free ligand overlap, which may suggest that the oxazoline nitrogen atom does not participate in the complexation. It explains the lack of enantiocontrolling ability of ligand **3a** in the nitroaldol reaction [6]. This complexation manner probably occurs for other not active ligands **3** as well. The presence of free ligands in the analyzed samples indicates that the complexes of ligands with $Cu(OAc)_2{\cdot}H_2O$ are not stable, and the equilibrium between the complex and ligand is shifted toward free ligand. ^{1}H NMR spectra were also obtained for complexes with other ligands, but they were usually difficult to analyze due to paramagnetic broadening of the signals. More detailed magnetic resonance studies, e.g. ^{15}N NMR of these complexes, were not conducted due to low concentrations of the complexes present in the samples and broadening of ^{1}H NMR signals.

Spectrophotometric investigations of complexes were further conducted. The electronic spectrum of ligand **1f** shows significant absorption bands at 288 and 325 nm attributed to π-π^* and n-π^* transitions, respectively (Figure 5). In the presence of copper, the band at 325 nm is shifted to 377 nm, which indicates the formation of complex. This band is associated with a broad shoulder at the red end of the spectrum (> 420 nm) (Figure 5).

The Yoe and Jones' mole-ratio method at constant concentration of Cu(II) (2×10^{-3} M) and varying concentrations (0.0 M to 5.2×10^{-3} M) of ligand **1f** was applied to determine the stoichiometry of complex **1f**–Cu (Figure 6). As can be seen, the absorption of the d-d band at 669 nm, assigned to copper(II) acetate, is decreasing with increasing ligand concentration, but it is not accompanied by shifting of the band (Figure 6C). This obviously indicates that Cu(II) ion is reduced to Cu(I) upon ligand-to-metal charge transfer.

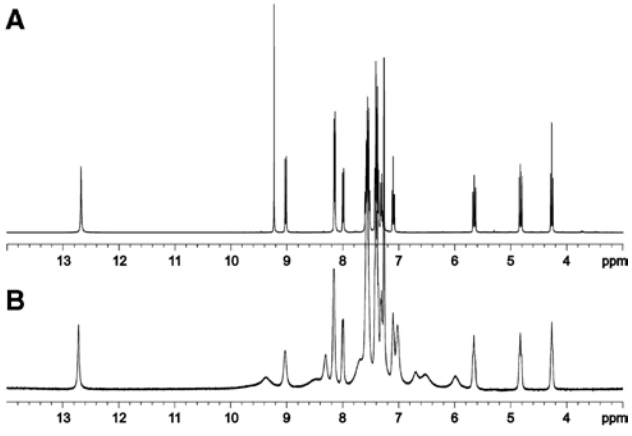


Figure 4 ^{1}H NMR spectra ($CDCl_3$, 400 MHz) of ligand **1f** (A) and complex **1f**–Cu formed *in situ* by mixing **1f** and $Cu(OAc)_2{\cdot}H_2O$ (B).

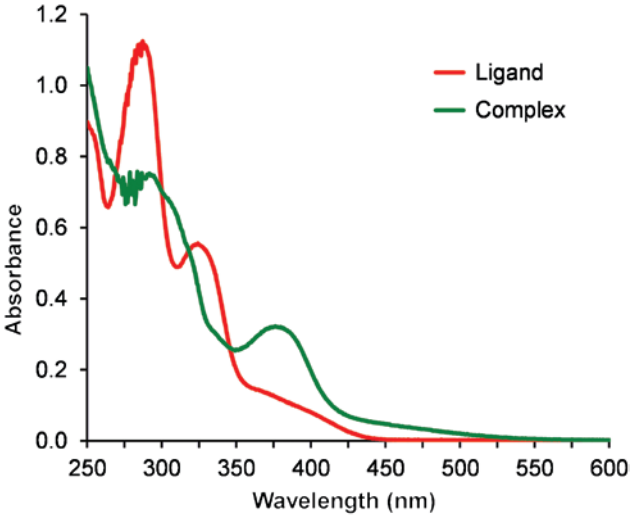


Figure 5 UV-vis spectra of ligand **1f** (4×10^{-5} M) in THF and complex **1f**–Cu formed *in situ* by mixing **1f** and $Cu(OAc)_2{\cdot}H_2O$ in THF.

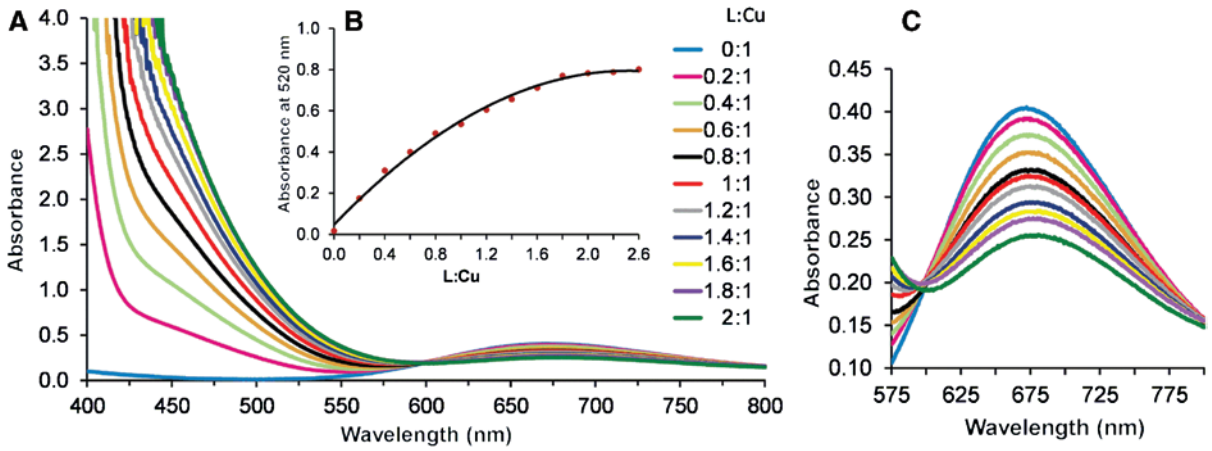


Figure 6 (A) Stoichiometry studies for **1f**–Cu complex at 520 nm using copper concentration of 2×10^{-3} M and varying concentrations (0.0 M to 5.2×10^{-3} M) of ligand **1f**. (B) Plot of the absorption at 520 nm as a function of L:Cu mole ratio. (C) Decreasing absorption of the d-d band of Cu(II) with increasing concentration of ligand.

The low-energy absorption, broad shoulder, present in the complex spectra (Figure 5) can be assigned to metal-to-ligand charge transfer (MLCT) transitions, which is a characteristic for Cu(I) complexes [10]. The absorption of the shoulder measured at 520 nm is increasing with increasing amount of ligand. The highest absorption is observed at a 2:1 ratio of L:Cu and it does not change on addition of larger amounts of ligand (Figure 6B). This study reveals a 2:1 (L:Cu) stoichiometry in the complex formed between ligand **1f** and Cu.

The complexes of ligands **1** with $Cu(OAc)_2{\cdot}H_2O$ were also studied by ESI-HR-MS. ESI is a sensitive ionization mode and thus considered as a very appropriate method for the investigation of complexes, although the ions in the gas phase can be different from those present in solution [11]. As the attempted isolation of complexes failed, samples obtained by mixing ligand with $Cu(OAc)_2{\cdot}H_2O$ in 2-propanol were subjected to mass spectrometry analysis after evaporation of 2-propanol. Thus, ESI-HR mass spectra of several complexes **1**–Cu were obtained. In all spectra, the presence of ions $[2L+Cu(I)]^+$ was observed. The mass spectrum of the **1f**–Cu complex shows signal at *m/z* 849.2462 corresponding to the calculated mass of $[2(\mathbf{1f})+Cu(I)]^+$. The signal of ion of *m/z* 873.2457 is observed in the spectrum of **1n**–Cu, which matches the value expected for $[2(\mathbf{1n})+Cu(I)]^+$. Analogous signals for ions with *m/z* 1001.3078 and *m/z* 809.3077 are present in the spectra of **1b**–Cu and **1i**–Cu, respectively. The mass spectra of the investigated complexes indicate the existence of $[2(L\text{-}H)+Cu(II)+H]^+$ ions corresponding to Cu(II) complexes as well, but the intensity is lower and is varied depending on the ligand. The lowest intensity of $[2(L\text{-}H)+Cu(II)+H]^+$ ion is observed for complexes **1f**–Cu and **1n**–Cu. Complex **2g**–Cu formed by the ligand with a pyridine ring instead of a 1,2,4-triazine ring was also investigated by ESI mass spectroscopy. The spectra indicate the formation of the Cu(II) complex predominantly by showing the signal for ion with *m/z* 716.1953 being nearly identical with the mass calculated for $[2(\mathbf{2g}\text{-}H)+Cu(II)+H]^+$. The presence of **2g**–Cu(I) complex cannot be definitely excluded as the signal corresponding to it may be hidden under the signal of the Cu(II) complex. It can be suggested that the presence of Cu(I) ions could be a result of a redox process which typically occurs with ESI conditions during the study [12]. However, the findings obtained from the UV-vis study suggest that Cu(I) ions originally exist in the samples subjected to ESI-MS analysis. The intensities of the peaks for ions of the complexes are very low in comparison with those of the free ligand ions $(L+H)^+$, which are the most abundant peaks in the spectra. Peaks for ions corresponding to complexes composed of one molecule of ligand are not present in the spectra of the analyzed samples. The mass spectrometry study confirms 2:1 (L:Cu) stoichiometry of complexes formed between ligands **1** and $Cu(OAc)_2{\cdot}H_2O$ and the existence of Cu(I) species in solutions of the samples.

The results of MS, UV-vis and ^{1}H NMR spectroscopic studies indicate that ligands **1**, **2** and **3** form different catalytic species with copper acetate. This may explain different behavior between the ligands in the asymmetric nitroaldol reaction: ligands **1** possess the highest enantiocontrolling ability, ligands **2** show significantly lower activity, while ligand **3** is not stereo-active in the reaction. The colors of 2-propanol solutions of complexes formed from ligands **1**, **2** and **3** suggest the oxidation state of the copper ion and the formation of different species.

Thus, the solution of complexes **1**–Cu is reddish brown, while the solutions obtained by mixing ligands **2** or **3** and copper acetate monohydrate are typically green due to the color of Cu(II) ions.

Based on the UV-vis, ^{1}H NMR and MS studies, we propose the following complexation mode of ligands **1** and Cu. Two ligand molecules coordinate to the copper(II) ion with the amino and the oxazoline nitrogen atoms, initially forming sterically crowded square planar complex which undergoes reduction of Cu(II) to Cu(I) and rearranges to a distorted tetrahedral four-coordinated geometry, typical of Cu(I) complexes [10, 13]. The process is associated with the secondary amino-group proton shift to the six-membered heterocycle nitrogen atom. The shifting is more favorable for ligands **1** with the 1,2,4-triazine ring where the N2 and N4 nitrogen atoms are the most likely to accept the proton. Due to the lack of suitable crystals for X-ray diffraction analyses of **1f**–Cu and **2g**–Cu complexes, molecular modeling studies were undertaken to confirm their predicted molecular structures from MS investigations. The molecular structures of complexes (Figure 7) were obtained using molecular mechanics calculations with the MM+ force field. In both complexes, the copper ion is coordinated to two N-atoms of the central secondary amine groups and two N-atoms of the oxazoline rings of the two bidentate **1f** and **2g** ligands. The CuN_4 unit adopts a slightly distorted tetrahedral geometry with Cu–N bonds within the range 1.823–1.832 Å in **1f** and 1.823–1.827 Å in **2g**. The N–Cu–N angles are between 101.10° and 116.13° in **1f** and 100.50° and 116.32° in **2g**. This calculated geometry for **1f**–Cu and **2g**–Cu complexes is the result of the parametrization used for the Cu-atom in the MM+ force field. However, these calculations show the possibility of the formation of stable complexes **1f**–Cu and **2g**–Cu with reasonable geometry for the nitroaldol reaction conditions.

The existence of two different species of Cu(I) and Cu(II) complexes is suggested based on the mass spectrometry study. More sterically hindered ligands **1** tend to form tetrahedral four-coordinated complexes with copper(I) ions. Less-crowded ligands **2** with an unsubstituted six-membered heterocyclic ring support square-planar geometry of complexes with copper(II), as suggested for complex **2g**–Cu on the basis of its MS spectrum. Formation of species with Cu(II) of different geometries can explain the lower enantiocontrolling activity of ligands **2**.

Taking into account the above findings, the catalytic nitroaldol reactions for several aldehydes were rerun using a 2:1 ratio of ligand **1f** and $Cu(OAc)_2{\cdot}H_2O$ (Table 2, enries 1–10).

The results thus obtained are comparable to those obtained in reactions conducted with 1:1 ratio of ligand **1f** and Cu [3]. As the yields and enantioselectivities were not improved using 2:1 ratio of ligand **1f** and $Cu(OAc)_2{\cdot}H_2O$, it can be suggested that under both conditions the same catalytic complex is formed. On the basis of the UV-vis and MS studies, a complex of stoichiometry 2:1 (**1f**:Cu) is postulated. Under both conditions, the complex is formed in the amount sufficient to catalyze the nitroaldol reaction with the same efficiency. According to the equilibrium established between ligand and complex, free ligand is

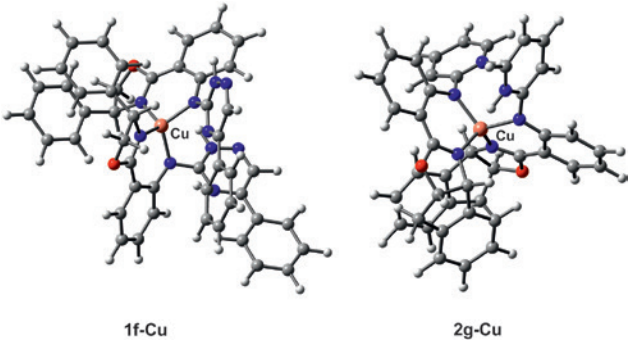
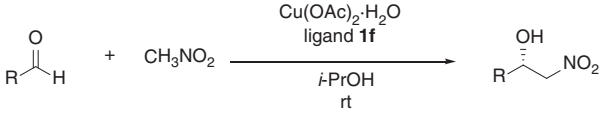


Figure 7 The structures of **1f**–Cu and **2g**–Cu complexes obtained after theoretical calculation using the molecular mechanics method.

Table 2 The catalytic enantioselective Henry reaction with 2:1 ratio of ligand **1f** and $Cu(OAc)_2{\cdot}H_2O$ and without $Cu(OAc)_2{\cdot}H_2O$.[a]



5a-j **6** **7a-j**

	R	Aldehyde	L (%)	Cu (%)	Product	Yield[b] (%)	ee[c] (%)
1	Ph	**5a**	10	5	**7a**	24	54 (*S*)
2	2-$NO_2C_6H_4$	**5b**	10	5	**7b**	68	59 (*S*)
3	3-$NO_2C_6H_4$	**5c**	10	5	**7c**	81	38 (*S*)
4	4-$NO_2C_6H_4$	**5d**	10	5	**7d**	83	35 (*S*)
5	2-ClC_6H_4	**5e**	10	5	**7e**	92	74 (*S*)
6	3-MeC_6H_4	**5f**	10	5	**7f**	13	50 (*S*)
7	2-$MeOC_6H_4$	**5g**	10	5	**7g**	53	64 (*S*)
8	2-BrC_6H_4	**5h**	10	5	**7h**	85	75 (*S*)
9	3-$MeOC_6H_4$	**5i**	10	5	**7i**	57	48 (*S*)
10	2-MeC_6H_4	**5j**	10	5	**7j**	51	48 (*S*)
11	3-$NO_2C_6H_4$	**5c**	5	0	**7c**	15	rac
12	4-$NO_2C_6H_4$	**5d**	5	0	**7d**	13	rac
13	2-ClC_6H_4	**5e**	5	0	**7e**	20	rac

[a]All reactions were performed on a 0.5 mmol scale in 2 mL of *i*-PrOH at room temperature for 98 h.
[b]Yields of isolated products.
[c]Enantiomeric excess was determined by HPLC using the Chiralcel OD-H column. The absolute configuration was assigned by comparing their specific rotations or the HPLC elution order with data from the literature.

present in the reaction mixture and it may therefore affect the reaction course as a catalyst. Different amounts of free ligand must be present in reaction run with 1:1 and 2:1 ligand-to-copper ratios, but as the results obtained under both conditions are similar, it can be suggested that free ligand does not have any impact on the reaction. To further investigate the issue, the nitroaldol reactions were carried out in the presence of ligand **1f** without addition of copper. The β-nitro alcohols thus formed were isolated as racemic mixtures in low chemical yields of 13%–20% (Table 2, entries 11–13), which is consistent with the suggestion that free ligand does not have any influence on the stereochemical outcome of the reaction.

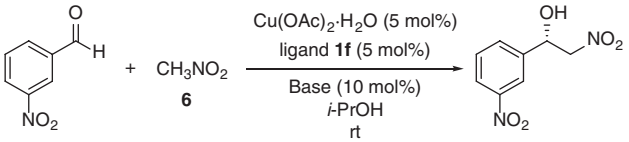
The nitroaldol reactions catalyzed by the 1,2,4-triazine-oxazoline ligands were run in the absence of base. Addition of an external organic base to the reaction catalyzed by **1f**-Cu has a negative influence on enantioselectivity. Weaker bases exhibit lower impact on enantioselectivity (Table 3, entry 1), while the stronger ones promote formation of product with optical purity lower than 20%. The strongest bases *N*,*N*-diisopropylethylamine (DIPEA) and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) direct the reaction toward racemic product (Table 3, entries 5 and 6).

Unfavorable impact of DIPEA and DBU can be a result of (i) deprotonation of not-coordinated nitromethane by stronger bases, which activates the unselective reaction route, (ii) competitive coordination to copper ion or (iii) coordination to **1f**–Cu complex instead of substrate which causes inactivation. Another disadvantage of using external bases can be promotion of elimination of water from the β-nitro alcohols.

In a reaction run without addition of base, the nitromethane must be deprotonated by acetate ion or by nitrogen atoms present in the six-membered heterocyclic ring of the ligand. Considering the basicity of the nitrogen atoms of the four heterocyclic systems present in ligands **1** and **2**, 1,2,4-triazine is the weakest base among them [14]. As ligands **1** with the lowest basic six-membered heterocyclic ring exhibit the highest enantiocontrolling ability, the nitrogen atoms of the six-membered heterocyclic ring cannot be responsible for deprotonation of the nitromethane. Thus, probably the acetate ion plays the role of a base.

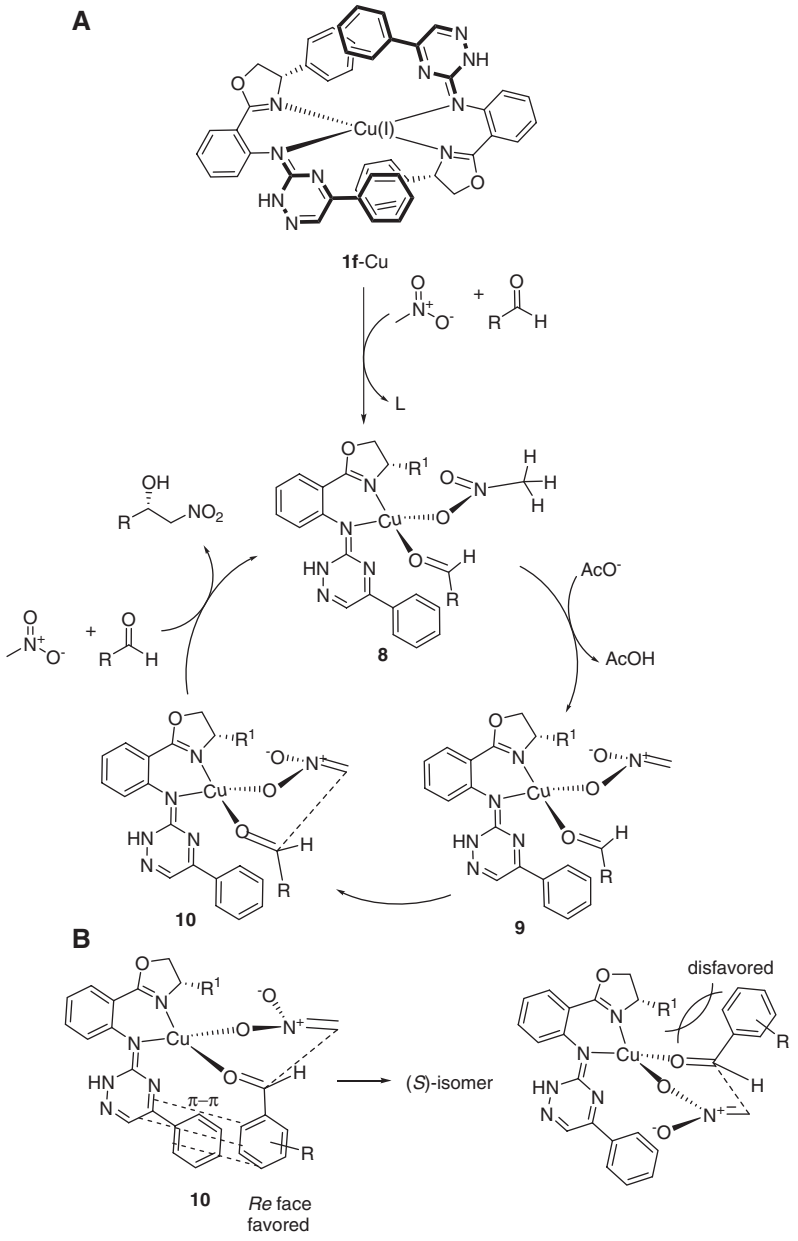
The ^{1}H NMR, UV-vis and MS studies revealed that the equilibrium between the complexes and ligands is strongly shifted toward free ligands, which indicates that the complexes are not stable. Therefore, all attempts to obtain single crystals from complexes suitable for X-ray analysis appeared impossible. Due to the lack of crystal structure of complexes, the transition state of the Henry reaction is discussed on the basis of the findings obtained from the ^{1}H NMR, UV-vis, MS studies, the X-ray diffraction analysis of ligands and the modeled complex obtained using MM calculations. Theoretical calculation is recognized as an efficient method to optimize geometry of complexes and to explain the mechanism of stereoinduction [15–17]. The suggested transition state and the catalytic cycle for the nitroaldol reaction catalyzed by **1**-Cu are shown in Scheme 1A. As the Cu(I) complexes easily undergo ligand exchange [18, 19], the replacing of one molecule of ligand with the aldehyde and nitromethane in **1**–Cu complex takes place to generate complex **8**. The nitroalkane is deprotonated by acetate ion, which gives state **9**, and finally, transition state **10** is formed. Then, the nitroaldol product is released and complex **8** is regenerated by binding molecules of nitromethane and aldehyde. Binding of the aldehyde to the southern position is probably energetically more favored as the process avoids the steric repulsion between the phenyl group of the aldehyde and the substituent in the oxazoline ring. In the nitroaldol reactions controlled by (*S*)-configured ligands **1**, the (*S*)-enantiomers of β-nitro alcohols are formed in excess. To ensure the stereoinduction, the nitronate must attack the aldehyde from the *Re* face (Scheme 1B). Possible π-π interactions between the 1,2,4-triazine ring or phenyl substituent in its C-5 position and the aldehyde phenyl ring keep the aldehyde in a position which makes the *Re* face

Table 3 The catalytic enantioselective Henry reaction in the presence of external base.[a]



	Base	pK_a	Yield[b] (%)	ee[c] (%)
1	NMM	7.4	66	41
2	DABCO	8.8	80	16
3	DMAP	9.2	79	14
4	TEA	10.8	82	8.5
5	DIPEA	11.4	56	6
6	DBU	12.5	74	rac

[a]All reactions were performed on a 0.5 mmol scale in 2 mL of *i*-PrOH at room temperature for 18 h.
[b]Yields of isolated products.
[c]Enantiomeric excess was determined by HPLC using the Chiralcel OD-H column. The absolute configuration was assigned by comparing their specific rotations or the HPLC elution order with data from the literature.
NMM, *N*-methylmorpholine; DABCO, 1,4-diazabicyclo[2.2.2]octane; DMAP, 4-(*N*,*N*-dimethylamino)pyridine; TEA, threethylamine; DIPEA, *N*,*N*-diisopropylethylamine; DBU, 1,8-diazabicyclo-[5.4.0]undec-7-ene.



Scheme 1 Proposed catalytic cycle (A) and transition state (B).

accessible for attack of the nitronate ion. The π-π interactions between the phenyl substituent in the 1,2,4-triazine C-5 position and the aldehyde phenyl group can also explain the higher activity of ligands with 1,2,4-triazine substituted in the C-5 position with a phenyl ring.

The more electron-withdrawing 1,2,4-triazine ring in complexes **1**–Cu makes the copper ion more acidic, which results in better activation of the coordinated aldehyde toward the attack of nitromethane. Ligands **2** possessing weaker electron-withdrawing heterocyclic rings are less activated, which can additionally explain the lower enantioselectivity observed in the reactions catalyzed by these ligands.

Conclusion

The X-ray diffraction analysis of model compounds **1f** and **2g** confirmed their molecular structures. Based on the geometry and conformation of **1f** and **2g** in the crystalline state, the possibility of metal complex formation involving the investigated oxazoline-based compounds as potential ligands was discussed. Formation of complexes between ligands **1** and copper is consistent with the analysis of ^{1}H NMR spectra, where the shifts of ligand proton signals are observed as a result of complexation. This conclusion is strongly supported by the analysis of UV-vis spectra. On the basis of the UV-vis and MS studies, the 2:1

(L:Cu) stoichiometry of complexes **1**–Cu was established. The study also revealed that Cu(II) ions are reduced to Cu(I) ions upon ligand coordination via ligand-to-metal charge transfer. Studies of ligands **1** support the formation of distorted tetrahedral Cu(I) complexes, while analysis of the ESI-MS spectra of ligands **2g** strongly suggests that these ligands are preferentially involved in chelation with copper(II). The possibility of formation of tetrahedral complexes is supported by theoretical calculation using the MM method. It is postulated that the higher enantiocontrolling ability of ligands **1** is the result of the high electron-withdrawing character of the 1,2,4-triazine ring and their tendency to form complexes with Cu(I) ion of tetrahedral geometry.

Experimental

^{1}H NMR spectra were recorded at 400 MHz on a Varian 400 spectrometer. Chemical shifts are reported relative to the solvent resonance as the internal standard. Mass spectra were obtained by using an LTQ Orbitrap Velos (Thermo Scientific) spectrometer. UV-vis spectra were obtained by using a Shimadzu UV-3600 spectrophotometer. Optical rotation values were measured at room temperature with a Perkin-Elmer polarimeter. The ee values were obtained by the high performance liquid chromatography (HPLC) (Knauer) analysis using a chiral stationary phase column (Chiralcel OD-H) eluting with isopropanol/hexanes. Thin layer chromatography (TLC) was carried out on aluminium sheets precoated with silica gel 60 F_{254} (Merck). Column chromatography separations were performed using a Merck Kieselgel 60 (0.040–0.060 mm).

X-ray structure determinations of 1f and 2g

X-ray diffraction data of **1f** and **2g** were collected at 120 K on the SuperNova X-ray diffractometer equipped with an Atlas S2 CCD detector; crystal sizes 0.45 × 0.05 × 0.02 mm (**1f**) and 0.32 × 0.08 × 0.05 mm (**2g**), CuKα (λ = 1.54184 Å) radiation, ω scans. The analytical numeric absorption correction using a multifaceted crystal model based on expression derived by Clark and Reid [20] was applied; the ratios T_{min}/T_{max} of 0.708/1.000 for **1f** and 0.867/0.971 for **2g** were obtained. Both structures were solved by direct methods using SHELXS-2013 [21] and refined by full-matrix least-squares with SHELXL-2014/7 [21]. All H-atoms were located by difference Fourier synthesis. The N-bound H-atom was refined freely. The remaining H-atoms were treated as riding on their C-atoms, with C–H distances of 0.93 (aromatic), 0.96 (CH_3), 0.97 (CH_2) and 0.98 Å (CH). All H-atoms were assigned U_{iso}(H) values of 1.5U_{eq}(N,C). The absolute configuration for both compounds was established from the absolute configuration of the substrate used for their synthesis and confirmed by anomalous dispersion effects with the Flack × parameter of −0.2(2) and 0.02(12) for 1331 and 1275 quotients for **1f** and **2g**, respectively [22]. All calculations were performed using the WINGX version 2014.1 package [23]. CCDC-1487643 (**1f**) and CCDC-1487644 (**2g**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk].

Crystal data of 1f $C_{24}H_{19}N_5O$, M = 393.44, orthorhombic, space group $P2_12_12_1$ a = 5.4030(2), b = 10.2366(3), c = 34.5542(10) Å, V = 1911.15(10) Å^3, Z = 4, d_{calc} = 1.367 mg m^{-3}, F(000) = 824, μ(Cu Kα) = 0.699 mm^{-1}, T = 120.01(10) K, 27621 measured reflections (θ range 4.50–76.61°, 3983 unique reflections (R_{int} = 0.077), final R = 0.044, wR = 0.107, S = 1.079 for 3625 reflections with $I > 2\sigma(I)$.

Crystal data of 2g $C_{21}H_{17}N_3O$, M = 327.38, orthorhombic, space group $P2_12_12_1$, a = 6.0870(1), b = 11.8809(1), c = 21.9053(2) Å, V = 1584.17(2) Å^3, Z = 4, d_{calc} = 1.373 mg m^{-3}, F(000) = 688, μ(Cu Kα) = 0.687 mm^{-1}, T = 120.01(10) K, 44278 measured reflections (θ range 4.04–76.24°), 3320 unique reflections (R_{int} = 0.108), final R = 0.045, wR = 0.091, S = 1.153 for 3171 reflections with $I > 2\sigma(I)$.

General procedure for the catalytic enantioselective Henry reaction

A mixture of $Cu(OAc)_2 \cdot H_2O$ (5.5 mg, 0.027 mmol, 5.5 mol%) and ligand **1f** (0.05 mmol, 5 mol%) in anhydrous isopropanol (2 mL) was stirred at room temperature for 4 h under argon atmosphere to give a reddish-brown solution. The aldehyde (0.5 mmol) and nitromethane (270 μL, 5 mmol) were added and the mixture was allowed to stand at room temperature for 4 days. Then the solvent was removed under reduced pressure and the product was isolated by column chromatography. The ee values of the nitroalcohols were determined by chiral HPLC analysis using the Chiralcel OD-H column. The absolute configurations of the products were assigned by comparing their specific rotations or the retention times in HPLC with the literature data.

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