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Evaluation of the enantioselectivity of new chiral ligands based on imidazolidine-4-one derivatives

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Abstract

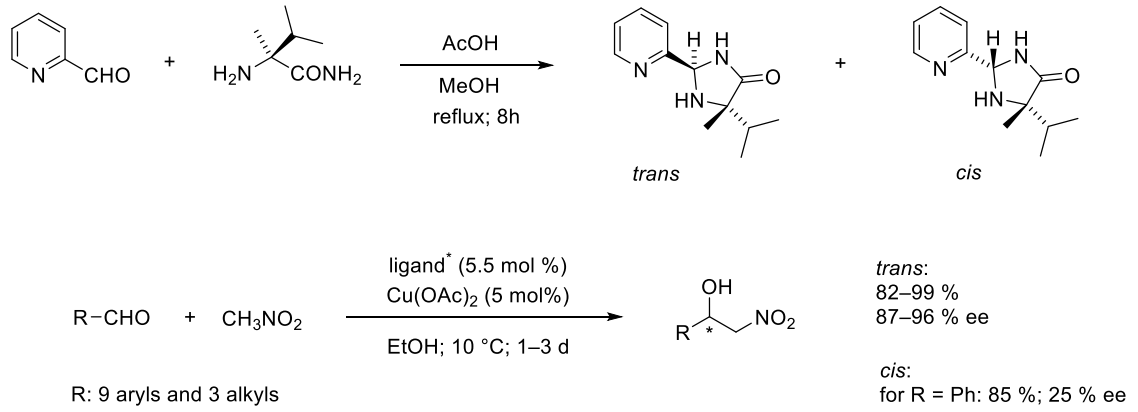
The new chiral ligands **I-III** based on derivatives of imidazolidine-4-one were synthesised and characterised. The catalytic activity and enantioselectivity of their corresponding copper(II) complexes were studied in the asymmetric Henry reaction. It was found out that the enantioselectivity of these catalysts is very high overall and depends on the relative configuration of the ligand used; *cis*-configuration of ligand affords the nitroaldols with major enantiomer *S*- (up to 97 % ee), whereas the application of ligands with *trans*-configuration led to nitroaldols with major *R*-enantiomer (up to 96 % ee). The "proline-type" ligand **IV** was also tested in asymmetric aldol reaction. Under optimised reaction conditions, aldol products with enantioselectivity of up to 91 % ee were obtained.

Keywords: Asymmetric Henry reaction; Asymmetric aldol reaction; Chiral ligands; Enantioselective catalysis; Imidazolidine derivatives

Introduction

The application of chiral metal complexes as an enantioselective catalyst is among the fundamental strategies for preparing compounds in non-racemic forms [1-4]. These complexes typically comprise a chelating chiral ligand capable of coordinating with a metal ion; otherwise, a metal atom itself constitutes a stereocentre [4]. The specific pairing of a chiral ligand and a metal ion is essential for the complex's catalytic characteristics and its effectiveness in asymmetric syntheses [1-3]. In recent years, our research group has synthesised a series of chiral ligands based on 2-(pyridine-2-yl)imidazolidine-4-one, differentiated by various substitutions at the imidazolidine ring [5-7]. Their copper(II) complexes were evaluated as efficient enantioselective catalysts, particularly in asymmetric Henry reactions (Scheme 1). Subsequent research has led to the development of various catalytic arrangements of the most enantioselective catalysts, including anchoring on polystyrene beads [8,9], magnetic nanoparticles [10], or block copolymers composed of PEG-poly(Glu) [11]. These modifications have facilitated the recycling of the catalysts, offering numerous advantages, including enhanced economic efficiency, eco-friendly practices, and reduced waste. Catalysts with the highest enantioselectivity have been employed in the synthesis of essential chiral intermediates for drug production, such as Amprenavir [12], Rivaroxaban [13,14], Linezolid [13], Salmeterol [7]. Therefore, chiral 2-(pyridine-2-yl)imidazolidine-4-one derivatives stand out as a prominent class of chiral nitrogen ligands in enantioselective catalysis.

The previous work; Ref. [5]:



Scheme 1. The preparation of 5-isopropyl-5-methyl-2-(pyridine-2-yl)imidazolidine-4-one derivatives and their application in asymmetric Henry reaction, described in the previous work; Ref. [5].

In this work, we focused on structurally modifying 2-(pyridine-2-yl)imidazolidine-4-one ligands to potentially expand the range of efficient catalysts. Our goal was to synthesise ligands featuring two chiral imidazolidine-4-one units linked to the pyridine ring at the 2- and 6-positions (Chart 1 – ligands **I** and **II**). These newly designed ligands represent tridentate entities and are comparable to well-known chiral ligands such as PyBOX [15] and PyBidine [16]. Additionally, we explored further modifications by substituting the pyridine moiety with an imidazole ring in ligand **III** (Chart 1), motivated by DFT calculations (see SI, part S3) which confirmed that imidazole has a similar donor ability to pyridine. This change reduces the ring size within the ligand structure, potentially increasing the space available for coordinating reacting species, thereby possibly enhancing catalytic activity and enantioselectivity. We also aimed to assess the impact of alkyl groups at the 5-position of the imidazolidine ring on the ligand's enantioselectivity. Hence, we developed a ligand incorporating an unsubstituted pyrrolidine ring instead of the imidazolidine unit (Chart 1 – ligand **IV**). This structure characterises a 'proline-type' derivative, enabling its use not only as a chiral metal complex catalyst but also as an enantioselective organocatalyst [17]. Accordingly, its application in

enantioselective organocatalysis, particularly in asymmetric reactions through “enamine activation”, warrants further investigation.

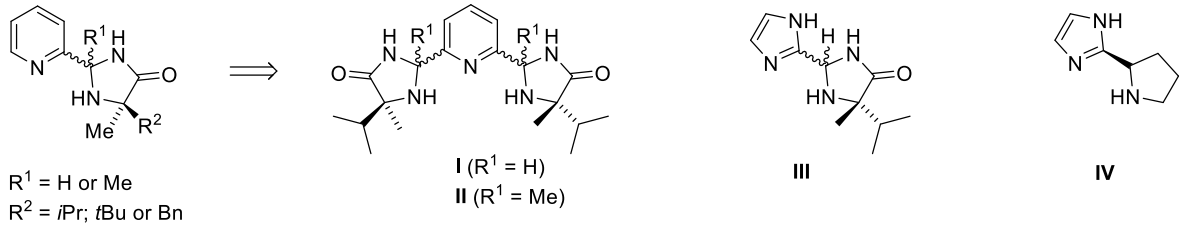
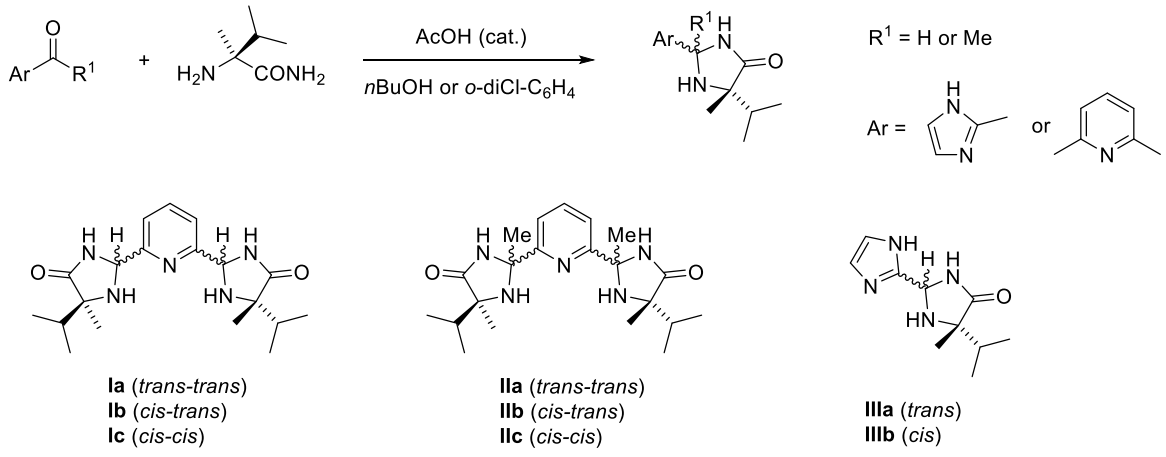


Chart. 1 The structure of newly designed ligands **I-IV**

Results and discussion

Synthesis of ligands

The 2,2´-(pyridine-2,6-diyl)-bis(imidazolidine-4-one) ligands **Ia-c** were prepared according to the modified protocol described previously (see Scheme 1) for the synthesis of analogous bidentate 2-(pyridine-2-yl)imidazolidine-4-one ligand (R^1 = H; R^2 = *i*Pr) [5]. The formation of the ligands **Ia-c** consists of the condensation reaction of pyridine-2,6-dicarbaldehyde with (*S*)-2-amino-2,3-dimethylbutanamide (Scheme 2).



Scheme 2. The synthesis of the ligands **I-III**.

To obtain the corresponding bis-(imidazolidine-4-one) derivatives in satisfactory yields and to avoid the appearance of mono-(imidazolidine-4-one) derivative intermediates in the crude product mixture, it was necessary to explore the appropriate reaction conditions. Key to the successful synthesis was the use of an excess of the 2-aminoamide reagent (3 equiv.; 1.5 equiv. to each carbonyl group) and an elevated reaction temperature of 80 °C. For this reason, the initially used solvent (MeOH) [5] needed to be replaced by *n*BuOH. The reaction time was extended to 120 h, under an inert argon atmosphere, to ensure complete conversion to ligands **Ia-c** while simultaneously preventing the formation of mono-(imidazolidine-4-one) intermediates and avoiding any undesirable oxidation to imidazoline-4-one derivative. This approach led to the high-yield production of ligands **Ia-c** (Chart. 2), with the diastereomers being formed in a ratio of 1:2:1 (**Ia**:**Ib**:**Ic**). The final isolation of each diastereomer was achieved by careful column chromatography on silica using a mixture of acetone, AcOEt, and MeOH (13/7/1) as the eluent. Multiple fractionation stages were necessary to effectively separate the mixture into distinct components.

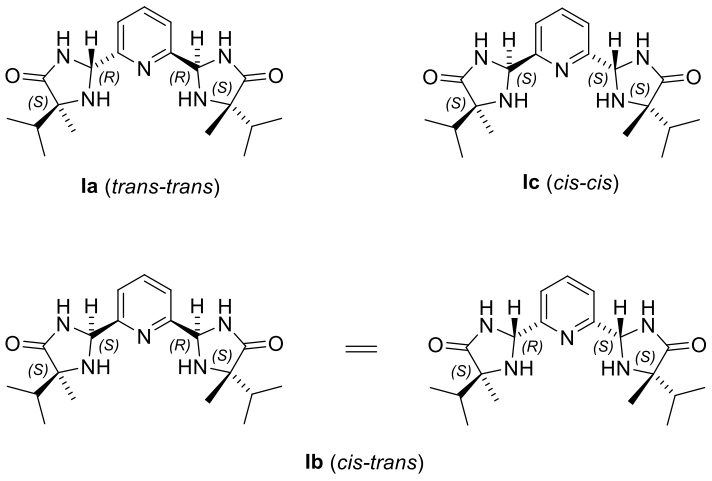


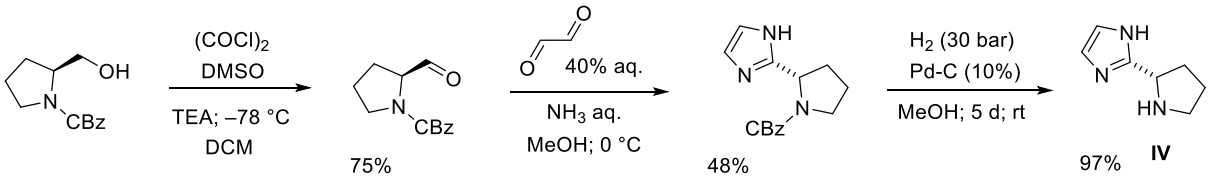
Chart. 2 The relative configuration at imidazolidine-4-one rings of ligands **Ia-c**

Inspired by the methodology outlined in reference [5] for the synthesis of a bidentate ligand (R^1 = Me; R^2 = iPr), and similar to the process used for the preparation of ligands **Ia-c**, ligands **IIa-c** were synthesised through a reaction between 2,6-diacetyl pyridine and (*S*)-2-amino-2,3-dimethylbutanamide (3 equiv.). A notable adaptation in this synthesis was the employment of *ortho*-dichlorobenzene as the solvent, enabling the reaction to proceed efficiently at the elevated temperature of 140 °C. TLC was used to monitor the reaction, with the disappearance of mono-(imidazolidine-4-one) derivatives observed after 96 h. The subsequent chromatographic separation (SiO_2; AcOEt/MeOH (20/1) yielded the individual diastereomers *trans-trans* (**IIa**), *cis-trans* (**IIb**), and *cis-cis* (**IIc**) in a ratio of 2:3:1, achieving an overall yield of 70%.

Building upon the methodologies employed for the earlier ligands and following the procedures outlined in reference [5] for synthesising 2-(pyridine-2-yl)imidazolidine-4-one analogues, the synthesis of ligands **IIIa-b** was achieved via a condensation reaction of (*S*)-2-amino-2,3-dimethylbutanamide with 1*H*-imidazole-2-carbaldehyde. Unlike the previous reaction conditions (for **Ia-c**; MeOH; 65 °C; 8h) that predominantly produced the Schiff base intermediate, the imidazolidine-4-one derivatives **IIIa-b** were successfully obtained under modified conditions. This involved refluxing in *n*BuOH for 17 h, leading to a good yield (66%) of the desired products. The individual epimers **IIIa** and **IIIb** (in the ratio of 3:4) were then effectively separated using column chromatography (SiO_2; acetone), ensuring the purity of the final compounds.

Following the established synthetic pathway detailed in references [18,19], compound **IV** was initially prepared starting from *N*-Boc-prolinol. The process involved synthesising (*S*)-2-(*N*-Boc-pyrrolidine-2-yl)-1*H*-imidazole. However, the deprotection step, traditionally conducted under conditions such as TFA/DCM [18] and $BF_3 \cdot Et_2O$ [19], resulted in the formation of numerous undesired by-products. To address this issue, we modified the method by replacing the Boc protecting group with a CBz group (Scheme 3). This alteration allowed for the

successful oxidation of *N*-CBz-prolinol via Swern oxidation, yielding the corresponding aldehyde with high efficiency (75 %) [20]. Subsequently, this aldehyde was converted to the imidazole derivative, following the original protocol, with a yield of 48% [18,19]. The final step involved hydrogenolysis for the deprotection of the pyrrolidine moiety, resulting in the formation of ligand **IV** as a pale-yellow oil. Notably, no racemisation was observed throughout the reaction process.



Scheme 3. The synthesis of the ligand **IV**.

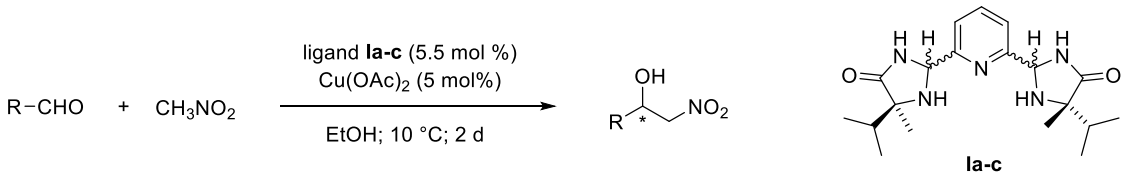
Enantioselective catalysis

With ligands **I-IV** in hand, their corresponding copper(II) acetate complexes were screened as enantioselective catalysts for the asymmetric Henry reaction. The series of nine different aldehydes (aliphatic, aromatic bearing electron-withdrawing or electron-donating group, heteroaromatic) was chosen for these studies. The reaction conditions (i.e. temperature, reaction time, amount of catalyst, solvent) were adopted from the pilot study [5] for relevant comparison of catalyst characteristics.

From Tables 1 and 2, which summarise results obtained using tridentate ligands **Ia-c** and **IIa-c**, it is evident that their copper(II) complexes' catalytic activity is comparable with the analogous bidentate ligands' complexes [5] (for TON and TOF parameters see SI, part S4). The conversions were very high in almost all cases under set reaction conditions, except for pivalaldehyde. Here, the low conversions could be explained by the sterical demand of aldehyde (R = *t*Bu), leading to suppressing its coordination with the complex. The ee values achieved with the complex of ligand **Ia** were variable (29-83 %), whereas better enantioselectivity was

found for less reactive aldehydes (aliphatic and bearing electron-donating group). Generally, this type of complex having *trans-trans* configuration (from **Ia**) is less enantioselective than the complex of bidentate analogue (87-96 % ee, see lit. [5]). Interestingly, the introduction of the methyl group at position 2- of the imidazolidine-4-one ring, i.e. ligand **IIa**, led to an improvement of enantioselectivity and the ee values obtained by its copper(II) complex were satisfactory (75-96 %). This phenomenon was more distinct in the case of the application complexes of ligands with *cis-trans* configuration (**Ib** vs. **IIb**). Whilst the complex of **Ib** exhibited only poor enantioselectivity, the other afforded the nitroaldols with ee values of 60-90 %. Finally, the complexes of the ligands with configuration *cis-cis* (**Ic** and **IIc**) were evaluated as the most efficient catalysts, producing nitroaldols with very high enantiomeric purity (approx. 90-95 % ee). This finding contrasts with the results obtained in the previous study [5], where the complex of the analogous bidentate ligand with *cis* configuration was found unsuccessful (~ 25 % ee; see SI, part S4).

Table 1. Asymmetric Henry reactions of various aldehydes with nitromethane catalysed by copper(II) complexes of ligand **Ia-c**



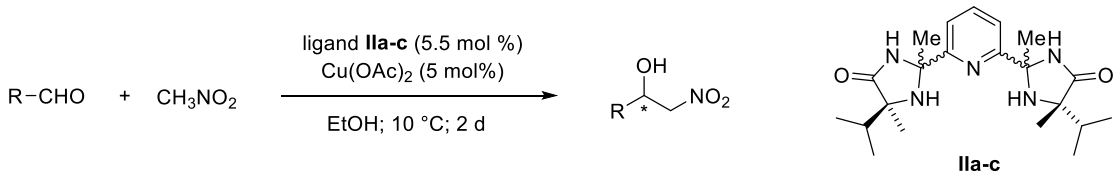
Aldehyde	Ligand Ia (*trans-trans*)		Ligand Ib (*cis-trans*)		Ligand Ic (*cis-cis*)	
R	**Conv[a] [%]**	**ee[b] [%]**	**Conv[a] [%]**	**ee[b] [%]**	**Conv[a] [%]**	**ee[b] [%]**
Ph	99	60 (*R*)	99	38 (*R*)	99	94 (*S*)
4-$NO_2C_6H_4$	99	29 (*R*)	99	8 (*R*)	99	91 (*S*)
2-$CH_3OC_6H_4$	99	80 (*R*)	99	*rac*	99	94 (*S*)
4-ClC_6H_4	99	52 (*R*)	99	7 (*R*)	99	95 (*S*)

2-thienyl	94	66 (*R*)	99	20 (*R*)	86	95 (*S*)
naphth-2-yl	96	69 (*R*)	94	25 (*R*)	94	93 (*S*)
$PhCH_2CH_2$	98	73 (*R*)	91	38 (*R*)	95	89 (*S*)
*t*Bu	35	80 (*R*)	30	41 (*R*)	32	96 (*S*)
*i*Pr	98	83 (*R*)	94	43 (*R*)	99	91 (*S*)

[a] The conversion was determined by ^{1}H NMR analysis of the crude product.

[b] The enantiomeric excess was determined by chiral HPLC.

Table 2. Asymmetric Henry reactions of various aldehydes with nitromethane catalysed by copper(II) complexes of ligand **IIa-c**



Aldehyde	**Ligand IIa (*trans-trans*)**		**Ligand IIb (*cis-trans*)**		**Ligand IIc (*cis-cis*)**	
R	**Conv[a] [%]**	**ee[b] [%]**	**Conv[a] [%]**	**ee[b] [%]**	**Conv[a] [%]**	**ee[b] [%]**
Ph	99	80 (*R*)	99	70 (*R*)	99	90 (*S*)
$4\text{-}NO_2C_6H_4$	99	75 (*R*)	99	60 (*R*)	99	82 (*S*)
$2\text{-}CH_3OC_6H_4$	99	96 (*R*)	99	77 (*R*)	99	86 (*S*)
$4\text{-}ClC_6H_4$	99	88 (*R*)	99	85 (*R*)	99	96 (*S*)
2-thienyl	95	90 (*R*)	98	86 (*R*)	97	97 (*S*)
naphth-2-yl	97	93 (*R*)	97	86 (*R*)	96	96 (*S*)
$PhCH_2CH_2$	92	75 (*R*)	95	87 (*R*)	97	91 (*S*)
*t*Bu	31	92 (*R*)	42	93 (*R*)	48	96 (*S*)
*i*Pr	98	96 (*R*)	99	90 (*R*)	93	96 (*S*)

[a] The conversion was determined by ^{1}H NMR analysis of the crude product.

[b] The enantiomeric excess was determined by chiral HPLC.

According to expectations [5], the complexes of the ligands **Ia** and **IIa** afforded the nitroaldols with the prevailing configuration *R*-, while the complexes of **Ic** and **IIc** with prevailing configuration *S*-. The application of the complexes of the ligands **Ib** and **IIb** (*cis-trans* form) also led to nitroaldols with some excess of *R*- enantiomer in all cases. The possible explanation of these results is illustrated in Chart 3, which shows plausible transition structures for the Henry reaction. To the Jahn-Teller effect, i.e. distortion of octahedral Cu(II) complex forming four equatorial and two perpendicular coordination sites [21], the effective transition state includes electrophile positioned in the equatorial site (strongly coordinated) and nucleophile in the perpendicular site (weakly coordinated) [22]. The most favourable orientation of aldehyde should be out of the ligand's molecular parts, thus forming *E*-configuration at the C=O bond. In this manner, the asymmetric induction results in the restricted addition of nitromethane influenced by imidazolidine-4-one moieties. The higher enantioselectivity of complexes of the ligands with *cis-cis* configuration could be explained by the fact that the larger (R_L) alkyl group is located toward the reactants. Thus, it blocks unfavourable *Si*-attack more effectively. Similarly, in the case of the complexes bearing *cis-trans* ligand can be preferred *Si*-attack due to the higher restriction of imidazolidine-4-one with *cis*-configuration, i.e. by more significant sterical demand of the R_L group.

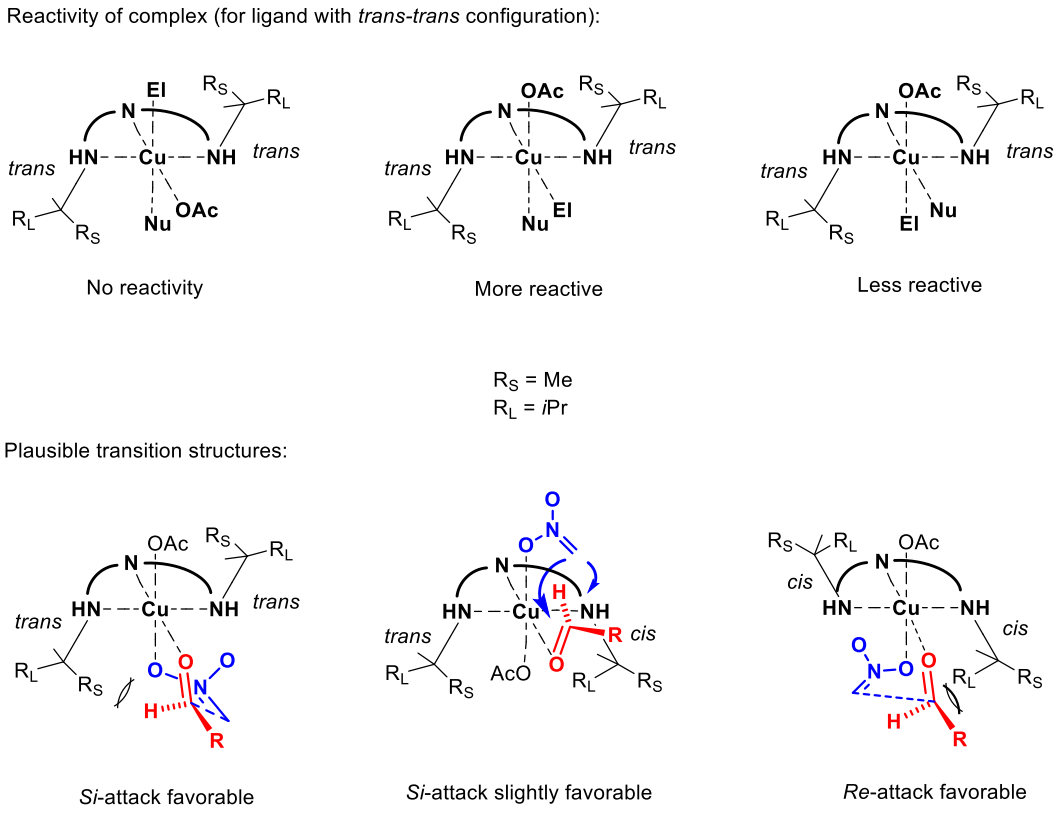
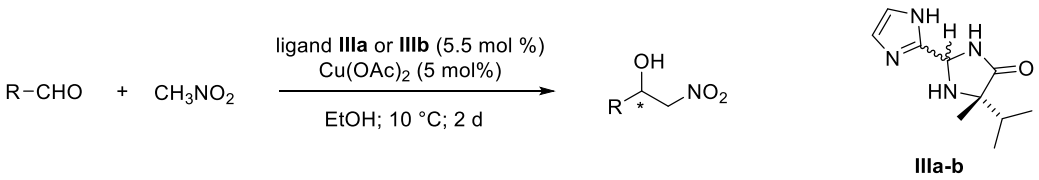


Chart. 3 Plausible transition structures for the Henry reaction.

Next, Table 3 summarises the results of Henry reactions obtained by catalysis with copper(II) complexes of the ligands **IIIa-b**. The mutual comparison of these catalysts with those composed of analogous 2-(pyridine-2-yl)imidazolidine-4-ones [5] follows several significant conclusions. For instance, the catalyst of ligand **IIIa** possesses lower catalytic activity than the pyridine derivative (for TON and TOF parameters see SI, part S4). The conversions were poor in the case of less reactive aldehydes, e.g. thiophene-2-carbaldehyde, and 3-phenyl propionaldehyde. To achieve satisfactory yields, the reaction time could be extended. Nevertheless, the ee values obtained by catalysts of **IIIa** vary in the range of 84-96 %; hence its enantioselectivity is comparable with the pyridine analogue [5]. Notably, the complex of ligand **IIIb** having *cis*-configuration is more enantioselective than pyridine derivative [5] (see SI, part S4); the ee values were overall high (74-92 %), however a little bit lower than achieved by the complex of ligand **IIIa** (Δ 1-15 % ee).

Table 3. Asymmetric Henry reactions of various aldehydes with nitromethane catalysed by copper(II) complexes of ligand **IIIa** and **IIIb**



Aldehyde	Ligand IIIa (*trans*)		Ligand IIIb (*cis*)	
R	Conv[a] [%]	ee[b] [%]	Conv[a] [%]	ee[b] [%]
Ph	63	89 (*R*)	57	86 (*S*)
4-$NO_2C_6H_4$	97	84 (*R*)	89	76 (*S*)
2-$CH_3OC_6H_4$	98	94 (*R*)	89	93 (*S*)
4-ClC_6H_4	82	89 (*R*)	76	85 (*S*)
2-thienyl	40	88 (*R*)	36	80 (*S*)
naphth-2-yl	63	89 (*R*)	63	84 (*S*)
$PhCH_2CH_2$	45	89 (*R*)	44	74 (*S*)
*t*Bu	62	96 (*R*)	49	92 (*S*)
*i*Pr	90	94 (*R*)	64	88 (*S*)

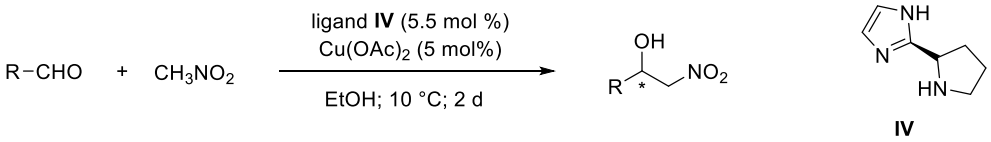
[a] The conversion was determined by ^{1}H NMR analysis of the crude product.

[b] The enantiomeric excess was determined by chiral HPLC.

Further, the copper(II) complex of ligand **IV** were also tested for asymmetric Henry reaction. The ligand **IV** structure arose from the ligand **IIIb** structure - the imidazolidine-4-one ring present at ligand **IIIb** was formally replaced by pyrrolidine one. Here, we presume the comparable coordinating ability of both species of heterocycles. However, the pyrrolidine cycle of ligand **IV** does not contain alkyl groups at position 5-. Therefore, the ee values obtained by the complex of ligand **IV** in the Henry reaction could be used for estimation of the impact of this substitution for the resulting enantioselectivity of studied ligands. The results summarised

in Table 4 follow that the complex of ligand **IV** is significantly less enantioselective (37-55 % ee) than the complex of ligand **IIIb**. Thus, the alkyl substitution at position 5- of the imidazolidine-4-one or pyrrolidine ring of the ligands **I-IV** can be considered a fundamental part of the ligand's structure, which enables them to possess high enantioselectivity. All nitroaldols were obtained with the excess of *S*-enantiomer, likewise in catalysis by copper(II) complexes of ligands **Ic**, **IIc** and **IIIb,** as well as ligands based on pyridine-(imidazolidine-4-one) [5-7] owned the *S*-configuration at the imidazolidine-4-one ring (see SI, part S4). Hence, the configuration of a ligand at position 2- determines the type of enantiomer of nitroaldol in excess and the environment around the stereogenic centre at position 5- affects the resulting value of ee.

Table 4. Asymmetric Henry reactions of various aldehydes with nitromethane catalysed by copper(II) complex of ligand **IV**



IV

Aldehyde	**Ligand IV**	
R	**Conv[a] [%]**	**ee[b] [%]**
Ph	97	50 (*S*)
4-$NO_2C_6H_4$	99	37 (*S*)
2-$CH_3OC_6H_4$	99	55 (*S*)
4-ClC_6H_4	91	50 (*S*)
2-thienyl	99	36 (*S*)
naphth-2-yl	98	46 (*S*)
$PhCH_2CH_2$	92	50 (*S*)
*t*Bu	40	52 (*S*)
*i*Pr	75	49 (*S*)

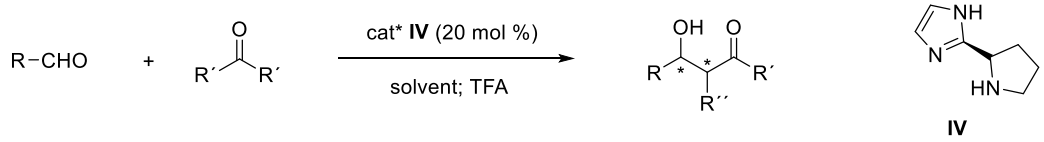
[a] The conversion was determined by ^{1}H NMR analysis of the crude product.

[b] The enantiomeric excess was determined by chiral HPLC.

The structure of compound **IV** is similar to the well-known organocatalyst – 5-(*S*)-pyrrolidine-2-yl-1*H*-tetrazole, which was successfully used in many asymmetric reactions via "enamine activation", especially in asymmetric aldol reaction [23-26]. Moreover, the **IV** was previously included in the study dealing with asymmetric cascade reaction (based on aldol reaction) of aldehydes with α-ketoacids producing chiral isotetronic acids. However, the application of compound **IV** as the organocatalyst in these reactions proceeded sluggishly, and the corresponding products were obtained in only moderate ees [19]. Herein, the aldol reaction was chosen as a standard asymmetric reaction to explore the catalytic features of the proline derivate **IV** in detail.

Although various proline derivatives have been described for use in asymmetric aldol reactions [27], the optimal reaction conditions for achieving maximal enantioselectivity and conversions vary and must be tailored to the specific catalyst used. Thus, the early attempts at aldol reaction of 4-nitrobenzaldehyde with cyclohexanone were performed to evaluate reaction parameters, i.e. solvent, reaction temperature, and amount of acidic additive (Table 5). Hence, using DMF at –25 °C was the most convenient condition regarding diastereo- and enantioselectivity and chemical yield. Next, the series of aromatic aldehydes with different substitutions were tested under the set reaction conditions. The yields decreased expectably in the range from aldehydes with EWG substituent to that with EDG. Thus, 4-tolualdehyde afforded the aldol product only with a moderate yield of 30 %; however, the diastereo- and enantioselectivity was satisfactory. A similar result was obtained in the reaction of 4-nitrobenzaldehyde with acetone. The comparison of **IV** with 5-(*S*)-pyrrolidine-2-yl-1*H*-tetrazole shows that both proline derivatives possess similar enantioselectivity. However, the compound **IV** is less catalytically active, probably due to the lower acidity of protonated 1*H*-imidazole than 1*H*-tetrazole [17].

Table 5. Asymmetric aldol reactions of various aldehydes with ketones catalysed by compound **IV**



IV

Aldehyde R	Ketone R´-CO-R´	Temp [°C]	Solvent	TFA [mol %]	Time [d]	Yield [%]	dr[a] (*antilsyn*)	ee[b] *(anti)* [%]
4-$NO_2C_6H_4$	-$(CH_2)_5$-	20	MeOH	20	5	88	2.25:1	73
4-$NO_2C_6H_4$	-$(CH_2)_5$-	3	MeOH	20	5	82	2.70:1	78
4-$NO_2C_6H_4$	-$(CH_2)_5$-	3	MeOH	40	5	89	2.60:1	82
4-$NO_2C_6H_4$	-$(CH_2)_5$-	3	DMF	20	3	96	2.70:1	83
4-$NO_2C_6H_4$	-$(CH_2)_5$-	–25	DMF	20	5	82	7.70:1	90
4-$NO_2C_6H_4$	-$(CH_2)_5$-	–25	DMF	40	5	95	20.0:1	89
4-$NO_2C_6H_4$	-$(CH_2)_5$-	–25	DMSO	40	5	40	2.50:1	81
4-$NO_2C_6H_4$	-$(CH_2)_5$-	–25	MeCN	40	14	26	6.70:1	91
4-CNC_6H_4	-$(CH_2)_5$-	–25	DMF	40	5	85	2.35:1	85
4-ClC_6H_4	-$(CH_2)_5$-	–25	DMF	40	5	88	4.00:1	82
Ph	-$(CH_2)_5$-	–25	DMF	40	5	56	11.0:1	86
4-$CH_3C_6H_4$	-$(CH_2)_5$-	–25	DMF	40	5	30	20.0:1	85
4-$NO_2C_6H_4$	CH_3-	–25	DMF	40	5	36	–	84

[a] The dr was determined by ^{1}H NMR analysis of the crude product.

[b] The enantiomeric excess was determined by chiral HPLC.

Conclusion

In this study, we successfully synthesised enantiomerically pure stereoisomers of 2,2´-(pyridine-2,6-diyl)-bis(imidazolidine-4-one) derivatives, **Ia-c** and **IIa-c**, analogous to well-known tridentate chiral ligands such as PYBOX [15] and PyBidine [16]. The copper(II) complexes of these ligands demonstrated remarkable enantioselectivity in asymmetric Henry reactions, achieving enantiomeric excess values exceeding 90% in numerous instances,

categorising them among the most efficient catalysts for this reaction type. A key finding of our research was the identification of position 2- on the imidazolidine-4-one unit as the crucial site for asymmetric induction. While the nature of the substituent at this chiral centre (i.e. hydrogen or methyl) influenced the catalytic results, it was always part of a more complex interplay involving the ligand-substrate combination, suggesting that the type of the substituent was not the sole determining factor.

Our investigation also revealed that the configuration of the latter chiral centre at position 5- significantly influences the catalyst's activity. While the bidentate 2-(pyridine-2-yl)imidazolidine-4-one ligands with a *trans* configuration at this position outperformed their *cis* counterparts (see SI, part S4), the tridentate ligands (**Ia-c** and **IIa-c**) exhibited higher enantioselectivity with a *cis* configuration at position 5- relative to position 2-. Additionally, when mixed configurations were present at position 2- in tridentate ligands (**Ib** and **IIb**), the 2*R*- configuration facilitated more effective chirality transfer.

Substituting the pyridine moiety with an imidazole in ligands **IIIa-b** led to a slower reaction rate compared to their pyridine counterparts. However, the *cis* diastereomer (**IIIb**) showed significantly enhanced enantioselectivity compared to its equivalent pyridine-based ligand with the same configuration (see SI, part S4). This change from pyridine to imidazole lowered the reaction rate but did not alter the critical role of configuration at position 2- in determining the final product's enantiomeric purity.

Furthermore, the study of "proline-type" derivative **IV** underscored the importance of position 2- in chirality transfer, although with reduced efficiency in the absence of a second stereogenic centre at position 5-. Nonetheless, **IV** proved to be an effective enantioselective organocatalyst in the asymmetric aldol reaction, matching the enantioselectivity levels of other proline-heterocycle derivatives [27].

Overall, our findings underscore the paramount importance of stereochemistry at position 2- in dictating enantioselectivity in chiral ligands. This study provides essential insights for the design of asymmetric catalysts, especially for Henry and aldol reactions.

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