UNIVERSITY OF PARDUBICE
FACULTY OF CHEMICAL TECHNOLOGY
Institute of Organic Chemistry and Technology

Ing. Gabriela Nováková

Recyclable Catalytic Systems for Asymmetric Henry Reaction

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Author: **Ing. Gabriela Nováková**

Supervisor: **Assoc. Prof. Ing. Pavel Drabina, Ph.D.**

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References

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Abstract

This dissertation is focused on the preparation and application of catalysts based on 2-(pyridine-2-yl)imidazolidine-4-thiones. The copper(II) complexes of the prepared imidazolidine-4-thiones were studied as the enantioselective catalysts for asymmetric Henry reaction. It was found out, that many of these catalysts afford 2-nitroalcohols with high enantioselectivity (up to 97 % ee). Further, the imidazolidine-4-thione ligands were anchored to swellable polystyrene supports and the subsequent reaction of modified polymers with copper(II) acetate gave the recyclable forms of catalysts. The catalytic activity, enantioselectivity and recyclability of prepared heterogeneous catalysts were studied. Another part of dissertation describes the development of synthetic procedure for the preparation of all stereomers of biologically active natural sphingoid bases – Clavaminol A and Xestoaminol C *via* Henry reaction. Subsequently, cytotoxic activity of individual stereomers was tested and evaluated in selected cancer cell lines.

Keywords

Henry reaction; Imidazolidine-4-thione derivatives; Enantioselective catalysis; Recyclable catalysts; 2-aminoalcohols; Sphingosine derivatives; Clavaminol A; Xestoaminol C

Abstrakt

Tato disertační práce je zaměřena na přípravu a použití katalyzátorů na bázi 2-(pyridin-2-yl)imidazolidin-4-thionů. Měďnaté komplexy připravených imidazolidin-4-thionů byly studovány jako enantioselektivní katalyzátory pro asymetrickou Henryho reakci. Bylo zjištěno, že tyto katalyzátory poskytují 2-nitroalkoholy s vysokou enantioselektivitou (až 97 % ee). Dále byly imidazolidin-4-thionové ligandy ukotveny na botnavé polystyrenové nosiče a následnou reakcí takto modifikovaných polymerů s octanem měďnatým byly připraveny heterogenní katalyzátory. Jejich katalytická aktivita, enantioselektivita a možnost recyklace byla studována na Henryho reakci. Další část práce byla věnována vývoji syntetického postupu vhodného pro přípravu všech stereoizomerů biologicky aktivních přírodních sfingosinových bazí, a to Clavaminolu A a Xestoaminolu C, s využitím Henryho reakce. Následně byla testována a vyhodnocena jejich cytotoxická aktivita na vybraných liniích nádorových buněk.

Klíčová slova

Henryho reakce; Imidazolidin-4-thionové deriváty; Enantioselektivní katalýza; Recyklovatelné katalyzátory; 2-aminoalkoholy; Sfingosinové deriváty; Clavaminol A; Xestoaminol C

Table of Contents

1. Aim of thesis

This dissertation is part of a long-term research proceeding on the Institute of organic chemistry and technology UPa, which deals with preparation and application of the enantioselective catalysts for asymmetric syntheses. It follows the previously published works, in which the enantioselective catalysts based on copper(II) complexes of 2-(pyridine-2-yl)imidazolidine-4-one derivatives were described.[1,2] Here, this research is focused on development of the analogous catalysts based on copper(II) complexes of 2-(pyridine-2-yl)imidazolidine-4-thiones. In addition, the dissertation also describes the application of the most efficient catalysts for the preparation of biologically active compounds, i.e. Clavaminol A and Xestoaminol C and their stereomers. These compounds should be prepared with the aim to evaluate their cytotoxic activity in selected cancer cell lines.

The aims of this thesis are summarized in these points:

1. The preparation and characterization of new chiral ligands, i.e. (2*R*,5*S*)- and (2*S*,5*S*)-5-isopropyl-5-methyl-2-(pyridine-2-yl)imidazolidine-4-thiones.

2. The study of catalytic activity and enantioselectivity of copper(II) complexes of prepared imidazolidine-4-thiones in asymmetric Henry reaction and comparison of determined catalytic parameters with those obtained with previously described catalysts.

3. The preparation of heterogeneous forms of the catalysts based on the copper(II) complexes of (2*R*,5*S*)- and (2*S*,5*S*)-5-isopropyl-2,5-dimethyl-2-(pyridine-2-yl)imidazolidine-4-thiones (prepared in my thesis)[2] by anchoring of them to different polystyrene supports (e.g. Merrifield™ resin and JandaJel™ resin).

4. The preparation of heterogeneous forms of the catalysts based on the copper(II) complexes of (2*R*,5*S*)- and (2*S*,5*S*)-5-isopropyl-5-methyl-2-(pyridine-2-yl)imidazolidine-4-thiones by anchoring of them to selected polystyrene support.

5. The study of catalytic activity, enantioselectivity and recyclability of the prepared heterogeneous catalysts and their mutual comparison.

6. The study of catalytic activity and enatioselectivity of the prepared catalysts as well as other efficient catalysts in the asymmetric Henry reaction of nitroethane with decanal and/or dodecanal.

7. The development of convenient synthetic method for preparation of all stereomers of Clavaminol A and Xestoaminol C based on asymmetric Henry reaction and the evaluation of cytotoxic activity of the individual stereomers in different cancer cell lines.

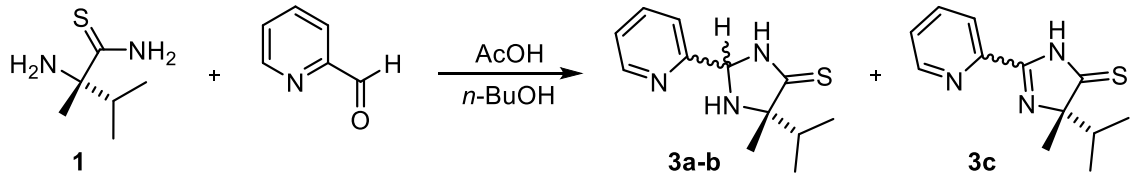
2. Introduction

The Henry reaction represents one of the fundamental organic synthetic tools for formation of carbon-carbon bond. It was discovered by Louis Henry in 1895.[3] Since then, this reaction has been intensively studied and used in many important syntheses.
The products of the asymmetric Henry reaction are non-racemic 2-nitroalcohols, which represent important building blocks. For instance, they can be utilized for the synthesis of many pharmaceutical substances. The most important derivatives of 2-nitroalcohols include chiral 2-aminoalcohols, which can be found in many biologically active compounds, e.g. (*R*)-Salmeterol,[4] Fosamprenavir,[5] epinephrine,[6] sphingosine derivatives[7,8] etc. The enantiomeric purity is important factor of their therapeutic effect.[6,9,10]
Asymmetric Henry reaction catalysed by enantioselective metal-based catalysts requires the application of a suitable chiral, enantiomeric pure ligand, in combination with metal ions. Among them, the Cu(II) complexes are the most successful.[1,11–13] During the last two decades, a lot of homogeneous enantioselective catalysts for asymmetric Henry reaction have been explored.[14] However, the applications of these catalysts are limited due to practical impossibility of their separation and reuse. The elimination of these disadvantages with regards to the economic and ecological aspects is an important trend in the research area of new catalytic systems development. The solution of these problems represents the immobilization of homogeneous forms of these catalysts by anchoring of them to the organic or inorganic carriers. The immobilized catalysts can be easily separated from the reaction mixture and then, reused in another catalytic cycles.

3. Results and discussions

3.1. Asymmetric Henry reaction

Enantiomerically pure (*S*)-2-amino-2,3-dimethylbutanethioamide (**1**) was the key intermediate for the preparation of (2*R*,5*S*)- (**2a**) and (2*S*,5*S*)-5-isopropyl-2,5-dimethyl-2-(pyridine-2-yl)imidazolidine-4-thione (**2b**), (2*R*,5*S*)- (**3a**) and (2*S*,5*S*)-5-isopropyl-5-methyl-2-(pyridine-2-yl)imidazolidine-4-thione (**3b**). This thioamide **1** was prepared by thionation of the corresponding enantiomerically pure amide using the procedure described previously for preparation of racemic form of **1**.[15,16] Imidazolidine-4-thione **2a** and **2b** (their synthesis was described in my thesis)[2] were prepared by acid-catalysed condensation of aminothioamide **1** with 2-acetylpyridine in 66% yields. The imidazolidine-4-thiones **3a** and **3b** were prepared by analogous procedure by condensation of pyridine-2-carbaldehyde with aminothioamide **1** in the presence of acetic acid under reflux in *n*-BuOH. The individual diastereomers **3a** (47 %) and **3b** (34 %) were separated by column chromatography (**Scheme 1**).



Scheme 1. Synthesis of (2*R*,5*S*)- (**3a**) and (2*S*,5*S*)-5-isopropyl-5-methyl-2-(pyridine-2-yl)imidazolidine-4-thione (**3b**) accompanied by production of imidazoline-4-thione **3c**

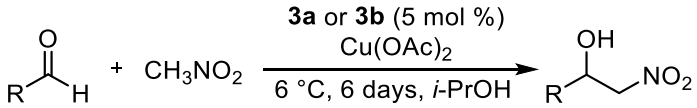
A certain amount of the oxidized form of the product, the imidazoline-4-thione derivative **3c**, was isolated (16%). The formation of this undesired by-product was suppressed by performance of the condensation reaction under argon atmosphere. It was found out, that during column chromatography the epimerization transformation of **3a** into **3b** and vice versa took place. This racemization process probably consists of acid-catalysed ring-opening of imidazolidine-4-thione cycle giving the corresponding Schiff base and its subsequent recyclization. This phenomenon has been already revealed during the characterization of derivatives **2a** and **2b** by ^{1}H NMR spectroscopy in $CDCl_3$ (containing traces of HCl) in previous work.[2] For this reason, it was necessary to carry out all manipulations with these ligands in neutral or basic media, where the epimerization does not take place.

The absolute configuration on the stereogenic centre at the 2-position of imidazolidine-4-thione derivatives **2**−**3** was determined by means of ^{1}H NMR 1D NOESY spectroscopy, which confirmed the previous findings,[1] that the derivatives with a *trans*-arrangement in imidazolidine-4-one or imidazolidine-4-thione cycle have a higher R_f value during chromatographic separation then the corresponding *cis*-forms.

At first, the catalytic activity and enantioselectivity of the *in situ* prepared homogeneous catalysts – the copper(II) complexes of ligands **3a-b** − was tested in the Henry reaction. The aim was the comparison of their catalytic parameters with the oxygen analogues (the copper(II) complexes of 2-(pyridine-2-yl)imidazolidine-4-ones)[1] and the copper(II) complexes of **2a-b**. Whilst Cu(II) complex of (2*R*,5*S*)-**3a** gave

corresponding 2-nitroethanols with the *R*-configuration in excess, the application of Cu(II) complex of (2*S*,5*S*)-**3b** gave the products with *S*-configuration in excess. The ee values in the products (**Table 1**) obtained by application of the catalyst **3a/Cu(OAc)$_2$** indicate, that its enantioselectivity (89–97% ee) is slightly higher than the enantioselectivity of analogous **2a/Cu(OAc)$_2$** complex containing the ligand with the methyl group at the position 2-. However, significant differences in catalytic activities of these complexes were found. While the catalyst **2a/Cu(OAc)$_2$** provided relatively good yields of the 2-nitroethanols, the catalyst **3a/Cu(OAc)$_2$** afforded only moderate yields. Further, the catalyst **3b/Cu(OAc)$_2$** exhibited more variable and relatively lower enantioselectivities (64–83% ee) with regard to the catalyst **3a/Cu(OAc)$_2$**. The obtained ee values and the yields are comparable with those values, found for analogous *cis*-form of catalyst **2b/Cu(OAc)$_2$**, in which the ligand contains the methyl group at position 2-. The catalytic activity and enantioselectivity of **3c/Cu(OAc)$_2$** was also tested. However, it afforded in the reaction of 2-methoxybenzaldehyde with nitromethane corresponding 2-nitroalcohol with low yield 17 % and unsatisfied ee (27 %).

Table 1. The survey of attempts of asymmetric Henry reaction of nitromethane with various aldehydes catalysed by **3a/Cu(OAc)$_2$** and **3b/Cu(OAc)$_2$**.

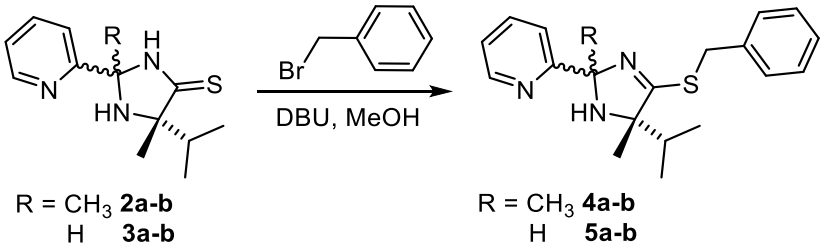


Entry	R	3a		3b	
		Yield (%)	ee[a] (%)	Yield (%)	ee[b] (%)
1	**Ph**	44	92	62	73
2	**2-$CH_3OC_6H_4$**	78	92	81	64
3	**4-ClC_6H_4**	39	92	53	72
4	**4-$NO_2C_6H_4$**	55	89	96	67
5	**4-PhC_6H_4**	34	92	44	71
6	***t*-Bu**	23	97	28	83
7	**thien-2-yl**	15	94	29	81
8	**naphth-2-yl**	25	90	50	73
9	**$PhCH_2CH_2$**	43	93	25	83

[a] *The reaction provides 2-nitroalcohol with **R** configuration in excess.*
[b] *The reaction provides 2-nitroalcohol with **S** configuration in excess.*

Further, benzylsulfanyl-imidazolidine derivatives **4**−**5** were prepared. The significance of their preparation lies in the fact, that their structures are very similar to the structure of the immobilized catalysts **10**−**13**. Therefore, their copper(II) complexes represent a homogeneous variant of target immobilized catalysts **10**−**13**, which enabled the comparison of the catalytic activity and enantioselectivity between homogeneous and heterogeneous catalytic systems. The compounds **4–5** were prepared by reaction of benzyl bromide with ligands **2**−**3** in the presence of DBU in methanol (**Scheme 2**). The chemoselectivity of benzylation reaction was confirmed by means of ^{1}H and ^{13}C NMR spectroscopy. The value of the chemical shift of the carbon atom

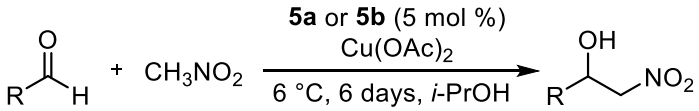
at the position 4- of the imidazoline ring was significantly changed (e.g., from 210.9 ppm for **3b** to 180.7 for **5b**).



Scheme 2. Synthesis of the imidazolidine-4-thiones **4**−**5a-b**

Table 2 summarizes the results of study of catalytic activity and enantioselectivity of the copper(II) complexes of **5a-b**. From the values of the chemical yields of the individual 2-nitroethanols is obvious, that the catalytic activity of **5a-b/Cu(OAc)$_2$** is significantly higher than the catalytic activity of **3a-b/Cu(OAc)$_2$**. This fact was confirmed by kinetic study, which describes the dependence of the conversion on the reaction time in the reaction of thiophene-2-carbaldehyde with nitromethane catalysed by both, **3a/Cu(OAc)$_2$** and **5a/Cu(OAc)$_2$**, respectively (**Figure 1**). The application of the catalyst **3a/Cu(OAc)$_2$** gave a conversion of only 13% after 96 h, while the catalyst **5a/Cu(OAc)$_2$** gave a conversion more than 90% after 48 h. This phenomenon can be explained by the possible participation of the sulphur atom of the complex **3a/Cu(OAc)$_2$** in coordination of copper atom of other molecule of the complex resulting in formation of oligomeric/polymeric adducts. Thus, sulphur behaves as a donor able to create a strong coordination bond with copper(II) ion.[17,18] The values of ee obtained by the application of **5a/Cu(OAc)$_2$** were generally high (82−97 % ee), but slightly lower than the ee values found with application of **3a/Cu(OAc)$_2$** (ca. Δ 1−7 % ee). Interestingly, the *cis*-isomer of the catalyst (**5b/Cu(OAc)$_2$**) afforded the 2-nitroalcohols with significant higher ee than the catalyst **3b/Cu(OAc)$_2$** (ca. Δ 15−29 % ee).

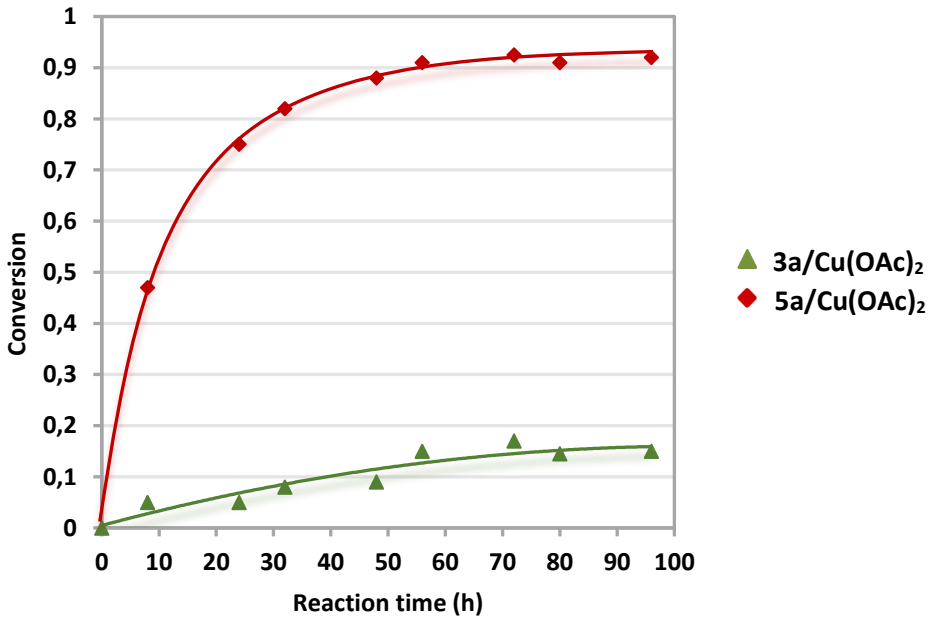
Table 2. The survey of attempts of asymmetric Henry reaction of nitromethane with various aldehydes catalysed by **5a/Cu(OAc)$_2$** and **5b/Cu(OAc)$_2$**.



Entry	R	5a		5b	
		Yield (%)	ee[a] (%)	Yield (%)	ee[b] (%)
1	**Ph**	98	84	98	90
2	**2-$CH_3OC_6H_4$**	98	83	99	93
3	**4-ClC_6H_4**	99	88	99	91
4	**4-$NO_2C_6H_4$**	99	82	99	89
5	**4-PhC_6H_4**	98	88	98	89
6	***t*-Bu**	99	96	99	98
7	**thien-2-yl**	91	85	93	89
8	**naphth-2-yl**	98	85	98	90
9	**$PhCH_2CH_2$**	99	92	99	91

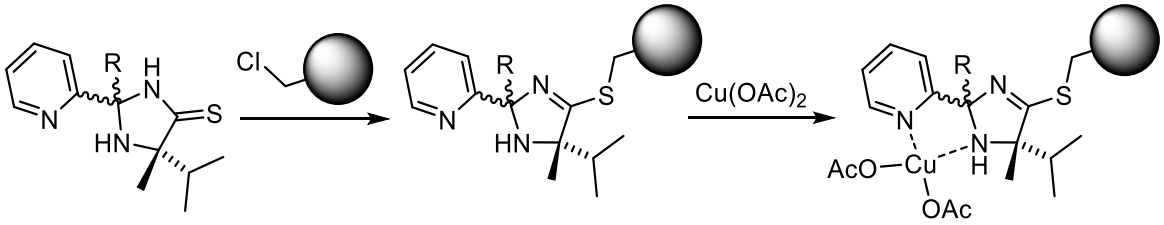
[a] *The reaction provides 2-nitroalcohol with **R** configuration in excess.*
[b] *The reaction provides 2-nitroalcohol with **S** configuration in excess.*

Figure 1. The time dependence (h) of conversion in the reaction of nitromethane with thiophene-2-carbaldehyde at 6 °C catalysed by **3a/Cu(OAc)$_2$** and/or **5a/Cu(OAc)$_2$**.



The preparation of the polymeric catalysts **10−13** consists in anchoring of the chiral ligands **2a-b** and **3a-b** on polymer carriers by reaction of their thiolactam group with chloromethyl groups of polymer carrier (**Scheme 3**). Three type of swellable copolymers of styrene and 4-vinylbenzyl chloride were used for immobilization of the ligands, which differed in the type of cross-linking agent and the amount of

chloromethyl groups. Within my thesis, the copolymer cross-linked with tetra(ethylene glycol)-bis(4-vinylbenzyl) ether (2 %) was used for preparation of the heterogeneous catalysts **10a-b**.[2] In this dissertation, the study was extended with another two commercially available copolymers, i.e. Merrifield™ resin (for **11a-b** and **13a-b** catalysts) containing 1 % of divinylbenzene as cross-linking agent and JandaJel™ resin (for **12a-b**), which was cross-linked by polytetrahydrofuran (2 %). Immobilization of the ligands **2a-b** and **3a-b** was performed at room temperature in DMSO in the presence of DBU. The prepared modified polymers **6−9** were characterized by elemental analysis and Raman spectroscopy (in the case of the polymer **9** by IR spectroscopy). Subsequently, copper(II) acetate was coordinated to the immobilized ligands **6−9** afforded the heterogeneous catalysts **10–13**. The amount of copper contained in the prepared catalysts was determined by atomic absorption spectroscopy.



R = CH_3 **2a-b**[2]
R = H **3a-b**

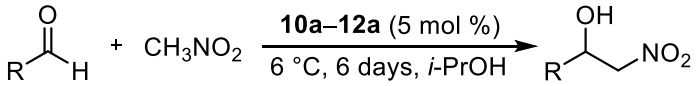
R = CH_3 **6a-b** ST-VBC-TEG[2]
7a-b Merrifield™ resin
8a-b JandaJel™ resin
R = H **9a-b** Merrifield™ resin

R = CH_3 **10a-b** ST-VBC-TEG[2]
11a-b Merrifield™ resin
12a-b JandaJel™ resin
R = H **13a-b** Merrifield™ resin

Scheme 3. Preparation of the immobilized catalysts **10−13**

Further, the immobilized catalysts **10−13** were studied as enantioselective catalysts for asymmetric Henry reaction. (**Tables 3−7, Figures 2−3**). The catalysts can be easily removed from the reaction mixture by simple filtration and reused in the next catalytic cycle. Thus, the Sheldon´s filtration tests for catalysts **10–13** were performed. The heterogeneous catalyst was separated from the reaction mixture in 24 h and the reaction course without the catalyst was monitored. The result of test was negative in all cases, hence, the reaction stopped completely after filtration of the catalyst. The study of catalytic activity and enantioselectivity of the catalysts **10−12** (derived from the chiral ligands **2a-b** containing methyl group at the position 2-) was performed in the Henry reactions of nitromethane with four selected aldehydes (**Tables 3−5**). The values of chemical yields indicated that the heterogeneous catalysts **10−12** afforded 2-nitroalcohols in high chemical yield and high enantioselectivity under set reaction conditions. It was found out, that type of polymeric support did not have a significant effect on the catalytic activity and enantioselectivity of the catalysts. The enantioselectivity of the immobilized catalysts **10a−12a** containing the *trans*-form of the ligand was lower than the enantioselectivity of homogeneous form of the catalyst **4a/Cu(OAc)$_2$** (ca. Δ 7% ee). On the other hand, the catalysts with *cis*-configuration of the ligand **10b−12b** gave 2-nitroalcohols with the ee values comparable to that of homogeneous variant of the catalyst **4b/Cu(OAc)$_2$**.

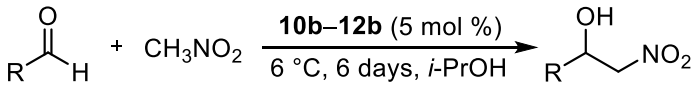
Table 3. The survey of attempts of the asymmetric Henry reaction of nitromethane with 2-methoxybenzaldehyde catalysed by the immobilized catalysts with *trans*-configuration **10a−12a**.



R (catal. cycle)	**10a**[2]		**11a**		**12a**	
	Yield (%)	**ee[a] (%)**	**Yield (%)**	**ee[a] (%)**	**Yield (%)**	**ee[a] (%)**
Ph (1.)	88	75	96	82	87	76
Ph (2.)	83	79	91	84	90	83
Ph (3.)	89	79	84	83	90	83
4-$NO_2C_6H_4$ (1.)	95	62	89	72	91	60
4-$NO_2C_6H_4$ (2.)	79	75	90	77	87	72
4-$NO_2C_6H_4$ (3.)	81	75	88	80	90	72
***t*-Bu (1.)**	93	92	98	95	90	94
***t*-Bu (2.)**	97	93	91	96	86	95
***t*-Bu (3.)**	98	92	99	95	94	96

[a] *The reaction provides 2-nitroalcohol with **R** configuration in excess.*

Table 4. The survey of attempts of the asymmetric Henry reaction of nitromethane with 2-methoxybenzaldehyde catalysed by the immobilized catalysts with *cis*-configuration **10b−12b**.



R (catal. cycle)	**10b**[2]		**11b**		**12b**	
	Yield (%)	**ee[a] (%)**	**Yield (%)**	**ee[a] (%)**	**Yield (%)**	**ee[a] (%)**
Ph (1.)	87	83	85	85	89	85
Ph (2.)	82	86	80	85	90	88
Ph (3.)	88	86	78	88	79	89
4-$NO_2C_6H_4$ (1.)	89	73	90	68	85	69
4-$NO_2C_6H_4$ (2.)	81	84	87	81	89	80
4-$NO_2C_6H_4$ (3.)	78	85	77	84	80	84
***t*-Bu (1.)**	95	94	99	95	95	96
***t*-Bu (2.)**	97	94	99	96	88	96
***t*-Bu (3.)**	98	95	94	94	95	97

[a] *The reaction provides 2-nitroalcohol with **S** configuration excess.*

The values of ee obtained in the first catalytic cycles were in many cases lower than those found in the following cycles (**Tables 3−5**). This finding can be explained by hypothesis, that the freshly prepared catalysts could contain copper(II) ions bounded not only to the chiral ligands, but also *via* non-specific coordination to the polymer carrier.

It was found out, that this problem can be solved by the activation of catalyst, consists in its treatment in the reaction medium for a so-called "induction period".[17,18] Such catalyst´s activation was tested on the polymers **10a-b** in the reaction of nitromethane with 2-methoxybenzaldehyde. The fresh catalysts **10a-b** were activated by suspending of them in the mixture of *i*-PrOH (1 mL) and nitromethane (0.5 mL) for 2 days at room temperature. After separation of the catalyst and subsequent application in the Henry reaction, the activated catalyst afforded the products with significantly higher ee than inactivated catalysts (ca. Δ 10 % ee).

The high recyclability of the heterogeneous catalysts **10−12** is shown in **Figure 2** and **Table 5**. From **Figure 2** is obvious, that no decrease of enantioselectivity of the catalysts **10a-b** took place even after ten catalytic cycles. Since seventh cycle, a slight decrease in conversion was observed. This decrease was probably caused by loss of catalyst during recycling procedure (filtration, decantation). Thus, it could be prevented by modification of the recycling process, for example by using "tea bag" method. The recyclability of the catalysts **11a-b** and **12a-b** was verified in five consecutive catalytic cycles of the reaction of nitromethane with 2-methoxybenzaldehyde (**Table 5**), in which almost the same results as in the study of recyclability of the catalysts **10a-b** were obtained.

Figure 2. The survey of the chemical yields of 1-(2-methoxyphenyl)-2-nitroethanol and the values of ee attained in the individual catalytic cycles with the application of the catalyst **10a**.[2]

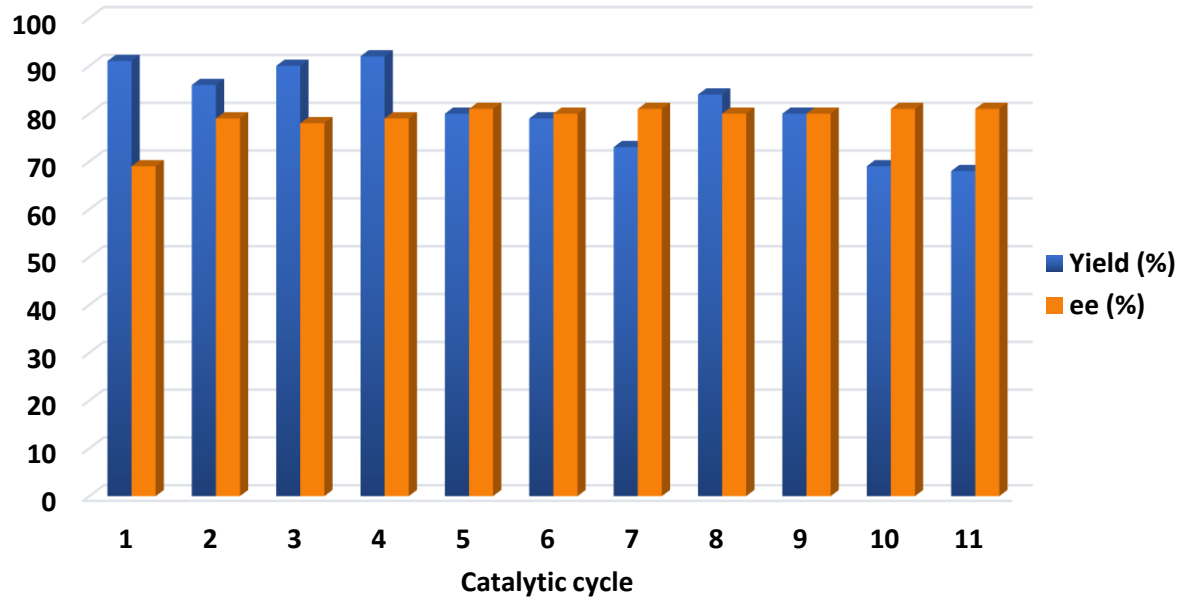
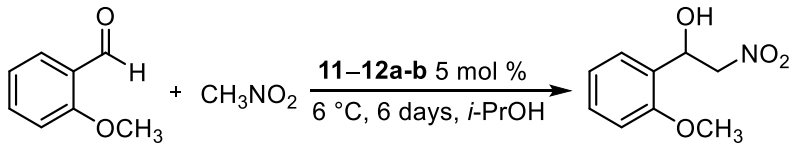


Table 5. The results of studies of recyclability of the immobilized catalysts **11a-b** and **12a-b**.



Catal. cycle	11a		12a		11b		12b	
	Yield (%)	ee[a] (%)	Yield (%)	ee[a] (%)	Yield (%)	ee[b] (%)	Yield (%)	ee[b] (%)
1.	84	81	90	74	80	83	91	85
2.	90	82	86	78	89	86	88	90
3.	87	84	89	78	82	88	89	90
4.	88	84	87	80	90	90	85	89
5.	79	84	91	80	85	89	89	90

[a] *The reaction provides 2-nitroalcohol with **R** configuration in excess.*
[b] *The reaction provides 2-nitroalcohol with **S** configuration in excess.*

Tables 3−5 show that the heterogeneous catalysts **10−12** exhibit higher catalytic activity than the homogeneous catalysts **2a-b/Cu(OAc)$_2$**. This fact was verified by kinetic study, which describes the dependence of conversion on reaction time in the reaction of 2-methoxybenzaldehyde with nitromethane catalysed by **2a/Cu(OAc)$_2$**, **4a/Cu(OAc)$_2$** and **10a** (**Figure 3**). From the curves is obvious, that the application of the heterogeneous catalyst **10a** gave the product with almost quantitative yield at the temperature of 6 °C after 10 h, whereas both types of the homogeneous catalysts afforded the conversion only 30 % at this time. After 30 h, the determined conversion was approximately 70 %. This phenomenon can be explained by possible formation of dimeric or oligomeric adducts[19,20] from the individual molecules of the **2a/Cu(OAc)$_2$**, resp. **4a/Cu(OAc)$_2$** complexes, in which the intermolecular coordination bond between the sulphur atom and the copper atom is formed. These dimeric or oligomeric complexes are probably catalytically inactive.[21]

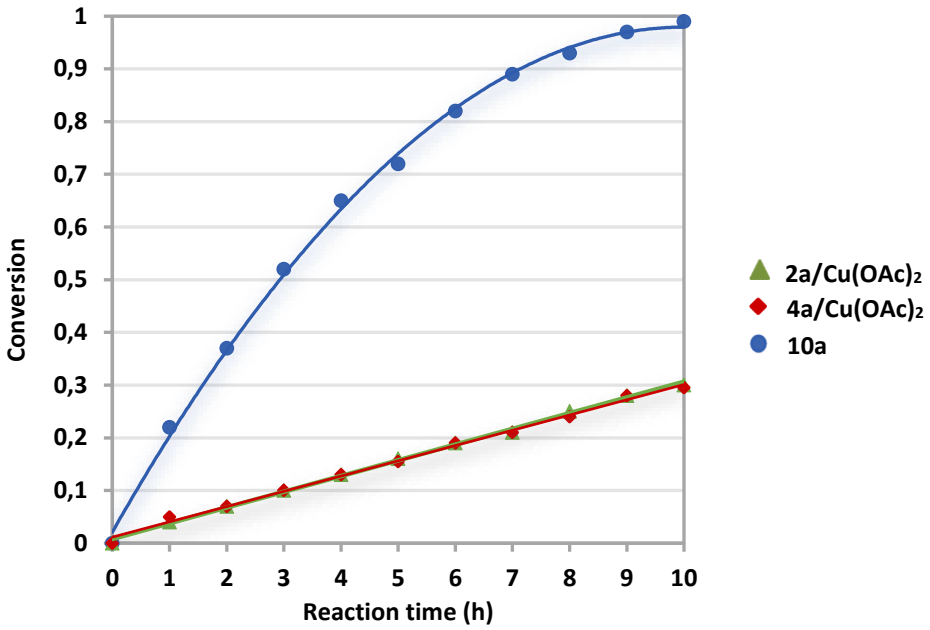
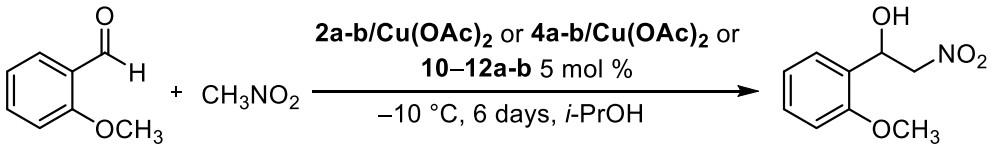


Figure 3. The time dependence (h) of conversion on reaction time in the reaction of nitromethane with 2-methoxybenzaldehyde catalysed by **2a/Cu(OAc)$_2$**, **4a/Cu(OAc)$_2$** and **10a** at 6 °C

With regards to the higher degree of catalytic activity of the heterogeneous catalysts **10**−**12**, their catalytic activity and enantioselectivity was also tested in Henry reaction at temperature of −10 °C (**Table 6**).

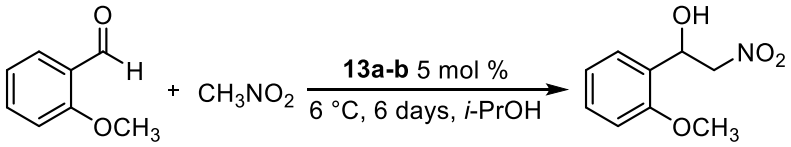
Table 6. The survey of attempts of the asymmetric Henry reaction of nitromethane with 2-methoxybenzaldehyde catalysed by **2a-b/Cu(OAc)$_2$**, **4a-b/Cu(OAc)$_2$** and **10**−**12a-b** at −10 °C.



Catalyst	Conversion (%)	Yield (%)	ee (%)
2a/Cu(OAc)$_2$	49	44	93 (***R***)
2b/Cu(OAc)$_2$	34	25	89 (***S***)
4a/Cu(OAc)$_2$	83	70	88 (***R***)
4b/Cu(OAc)$_2$	89	75	91 (***S***)
10a	99	89	83 (***R***)
10b	99	86	91 (***S***)
11a	72	65	89 (***R***)
11b	89	79	91 (***S***)
12a	99	90	86 (***R***)
12b	99	88	90 (***S***)

The values of ee, obtained in all performed attempts at –10 °C, show that the enantioselectivity of all tested catalysts increased (up to 93 % ee). Moreover, the heterogeneous catalysts **10−12** afforded satisfied values of conversions (72−99 %) even under these reaction conditions. From these findings follows that the application of homogeneous forms of the catalysts **2a-b/Cu(OAc)$_2$** is better at 6 °C due to their lower catalytic activity and sufficient enantioselectivity. Contrary, in the case of the immobilized catalysts **10−12** possessing higher catalytic activity, it is possible to use them at lower reaction temperature (−10 °C), what enhances their enantioselectivity.
The polymeric catalysts **10−12** were evaluated as efficient enantioselective catalysts in the Henry reaction, thus, analogous catalysts **13a-b** (based on the ligands **3a-b**) were further prepared and studied. The catalytic activity and enantioselectivity of the catalysts **13a-b** was tested in the reaction of nitromethane with 2-methoxybenzaldehyde at the temperature of 6 °C. Under this conditions, quantitative yields of corresponding 2-nitroalcohols were observed. Unfortunately, the prepared 2-nitroalcohols were obtained as racemates, because an epimerization or an oxidation of the catalysts **13a-b** probably occurred during their preparation and/or purification. The immobilized catalysts **13a-b** were also prepared under inert reaction conditions and their subsequent purification was carried out by carefully washing with methanol at room temperature. The results of the catalytic activity and enantioselectivity of the catalysts **13a-b** prepared by this way are shown in **Table 7**. The catalysts **13a-b** provided the products with significantly lower enantioselectivity in the first catalytic cycle (64 % ee for **13a** and 59 % ee for **13b**) than homogeneous variant of the catalysts **5a-b/Cu(OAc)$_2$** (Δ ca. 30 % ee). Further decrease in enantioselectivity of the catalysts **13a-b** was observed in each subsequent catalytic cycle (Δ ca. 2–3% ee). From these findings is obvious, that certain modification of ligands in the polymers **13a-b** (epimerization or oxidation) occur during their application under set reaction conditions. Therefore, the attempts of asymmetric Henry reaction were also performed in an argon atmosphere, but this change in reaction conditions did not produce satisfactory results (**Table 7**).

Table 7. The survey of attempts of the asymmetric Henry reaction of nitromethane with 2-methoxybenzaldehyde catalysed by the immobilized catalysts **13a-b**.



Catal. cycle	13a		13b	
	Yield (%)	ee[a] (%)	Yield (%)	ee[b] (%)
1.	97	64	96	59
2.	97	63	82	51
3.	92	60	85	48
4.	92	58	80	45
5.	55	48	59	42
1.[c]	84	58	86	40
2.[c]	76	62	71	37
3.[c]	74	50	70	38

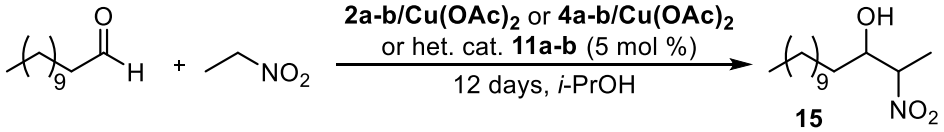
[a] *The reaction provides 2-nitroalcohol with **R** configuration in excess.*
[b] *The reaction provides 2-nitroalcohol with **S** configuration in excess.*
[c] *The reactions were performed under argon atmosphere with the catalysts **13a-b** prepared under inert reaction conditions.*

From the above results can be concluded, that the heterogeneous catalyst **13a-b** are not useful recyclable catalysts for asymmetric Henry reaction in contrast with the catalysts **10**−**12**. Thus, in the further research exclusively the immobilized catalysts **11a-b** were used, because they do not need to pass through "the catalyst´s activation".

3.2. Preparation and cytotoxic activity of all stereomers of Clavaminol A and Xestoaminol C

The next part of this work was focused on the application of the most efficient catalysts based on 2-(pyridine-2-yl)imidazolidine-4-thione derivatives for the preparation of the chiral compounds possessing interesting biological activity (e.g. significant cytotoxic activity, antimicrobial activity etc.) − Clavaminol A ((2*R*,3*S*)-2-aminododecan-2-ol) and Xestoaminol C ((2*S*,3*R*)-2-aminotetradecan-2-ol). The aim of this work was not only preparation of the naturally occurring stereomers in high enantiomeric purity, but also all the others, which still have not been described. For this reason, the choice of catalysts was done with respect to requirements, that they should provide 2-nitroalcohols with sufficiently abundance of both diastereomers (*anti*/*syn*) and high enantioselectivity for each enantiomeric pair. In the previous study[2] was confirmed, that the catalysts **2a-b/Cu(OAc)$_2$** and **4a-b/Cu(OAc)$_2$** provided corresponding 2-nitroalcohols derived from nitroethane and benzaldehydes with high enantioselectivity (up to 92 % ee) and dr ca. 2.0/1.0 (*anti*/*syn*). Therefore, these catalysts, together with the heterogeneous variant **11a-b**, were chosen for the preliminary study of the asymmetric Henry reaction of nitroethane with dodecanal, in which the optimization of reaction conditions was performed (**Table 8**).

Table 8. Optimization of reaction temperature for asymmetric Henry reaction of dodecanal with nitroethane catalysed by **2a-b/Cu(OAc)$_2$**, **4a-b/Cu(OAc)$_2$** and **11a-b**.



15

Catalyst	Temperature (°C)	Yield (%)	dr *anti:syn*	ee[a] (%) *anti*	ee[b] (%) *syn*
2a/Cu(OAc)$_2$	20	98	1.0:3.4	85	87
2a/Cu(OAc)$_2$	10	99	1.0:4.0	85	90
2a/Cu(OAc)$_2$	6	96	1.0:4.3	88	93
2a/Cu(OAc)$_2$	0	90	1.0:4.5	84	93
2b/Cu(OAc)$_2$	20	72	1.0:3.4	−10	−60
2b/Cu(OAc)$_2$	10	72	1.0:3.7	−51	−76
2b/Cu(OAc)$_2$	6	71	1.0:4.3	−58	−80
2b/Cu(OAc)$_2$	0	45	1.0:4.2	−58	−76
4a/Cu(OAc)$_2$	20	99	1.0:2.0	80	81
4a/Cu(OAc)$_2$	10	99	1.0:4.0	83	90
4a/Cu(OAc)$_2$	6	99	1.0:4.0	83	92
4a/Cu(OAc)$_2$	0	95	1.0:4.3	85	92
4b/Cu(OAc)$_2$	20	99	1.0:2.2	−72	−77
4b/Cu(OAc)$_2$	10	98	1.0:3.6	−84	−89
4b/Cu(OAc)$_2$	6	66	1.0:4.0	−84	−92
4b/Cu(OAc)$_2$	0	57	1.0:4.3	−82	−92
11a	6	99	1.0:4.0	84	91
11a	−10	60	1.0:4.4	84	92
11b	6	99	1.0:4.1	−83	−92
11b	−10	56	1.0:4.5	−84	−93

[a] *The ee for anti-diastereomer is expressed as (2S,3R) – (2R,3S)*
[b] *The ee for syn-diastereomer is expressed as (2R,3R) – (2S,3S)*

The performed attempts of the Henry reaction of dodecanal with nitroethane catalysed by the catalysts **2a-b/Cu(OAc)$_2$**, **4a-b/Cu(OAc)$_2$** and **11a-b** showed, that the reaction temperature has significant influence on chemical yields of the 2-nitroalcohol **15** and enantioselectivity of the used catalyst. The homogeneous forms of catalysts gave practically quantitative yields at room temperature (except of **2b/Cu(OAc)$_2$**), but the enantioselectivity was only moderate, especially for the catalyst **2b/Cu(OAc)$_2$**. The attempts performed at 0 °C resulted in lower yields of the 2-nitroalcohol, but high ee values were observed. On the other hand, in the attempts carried out at 10 °C were achieved satisfactory chemical yields, nevertheless, the 2-nitroalcohol **15** had slightly lower values of ee. Finally, the reaction temperature of 6 °C was evaluated to be a good compromise to achieve the high chemical yields of the 2-nitroalcohol **15** as well as

the enantioselectivity of used catalyst. In previous chapter was mentioned, that the heterogeneous catalysts **11a-b** exhibited high catalytic activity even at −10 °C, hence, these reaction conditions were also tested in the reaction of nitroethane with dodecanal. However, the significant reductions in chemical yields (99% vs. 60% for **11a**; 99% vs. 56% for **11b**) were observed, unfortunately, without any positive effects on the enantioselectivity of the catalysts. With regards to these findings, the reaction temperature of 6 °C was considered as the most convenient also for the heterogeneous catalyst **11a-b.** The diastereoselectivity of the individual catalysts **2a-b/Cu(OAc)$_2$**, **4a-b/Cu(OAc)$_2$** and **11a-b** differs only negligible and as expected, it increased with decreasing temperature. The major diastereomer in the 2-nitroalcohol **15** determined by ^{1}H NMR spectroscopy was *syn*-isomer.

In addition, the copper(II) complexes of the other enantioselective catalysts (**Figure 4**) were tested in the Henry reaction of nitroethane with dodecanal and/or decanal. The studied series of catalysts included not only the copper(II) complexes of the previously prepared 2-(pyridine-2-yl)imidazolidin-4-ones,[1] but also the copper(II) complexes of some commercially available chiral ligands, i.e. bisoxazolines,[12,22] and alkaloid sparteine.[4,23] **Table 9** summarizes the values of chemical yields and ee of 2-nitroalcohols **14-15** prepared in Henry reaction catalysed by the copper(II) complexes of above mentioned ligands. From the results is obvious, that the best enantioselectivity was attained with the catalyst **2a/Cu(OAc)$_2$** (*trans*-isomer of ligand). Unfortunately, although the catalyst **2b/Cu(OAc)$_2$** (*cis*-isomer of ligand) provided the 2-nitroalcohols **14-15** with the prevailing enantiomers having opposite configurations, i.e. (2*R*,3*S*)- and (2*S*,3*S*)-, only low enantioselectivities and low chemical yields were found. Similar results were obtained by modified catalysts, in which the ligands **2a** and **2b** were complexed with copper(II) chloride and TEA.[4,24]
In the case of the homogeneous catalysts **4a/Cu(OAc)$_2$** resp. **4b/Cu(OAc)$_2$** and the heterogeneous catalysts **11a-b** the 2-nitroalcohols **14-15** were obtained with the same ee values (*anti*- 84% ee; *syn*- 92% ee, *cis*-forms afforded the opposite enantiomers in excess). Other catalysts were not sufficiently enantioselective, except **L*4/Cu(OAc)$_2$** (*anti*- 89% ee; *syn*- 90% ee). Nevertheless, this catalyst provided the products with lower chemical yield (64–72%). Moreover, the application of **L*4/Cu(OAc)$_2$** for preparation of the 2-nitroalcohols **14-15** in multi-gram scale was unfavourable with regards to its relatively high cost. Hence, the recyclable catalysts **11a-b** were considered as more convenient.

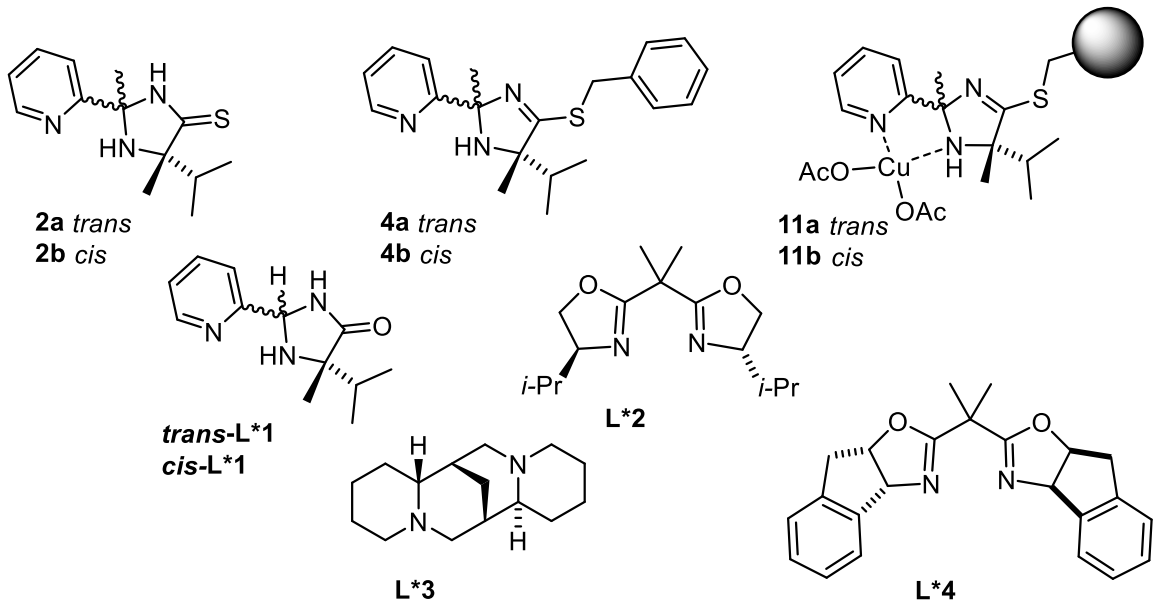
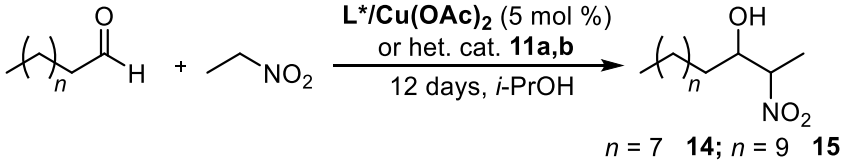


Figure 4. The survey of chiral ligands whose copper(II) complexes were tested for the asymmetric Henry reaction of decanal and/or dodecanal with nitroethane.

Table 9. The survey of attempts of the asymmetric Henry reaction of decanal and/or dodecanal with nitroethane catalysed by different chiral copper(II) complexes



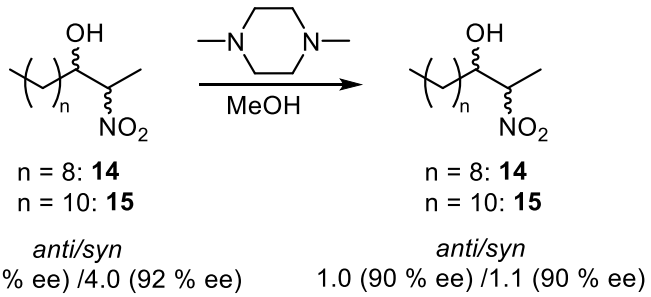
2-nitrododecan-3-ol (**14**) 2-nitrotetradecan-3-ol (**15**)

Catalyst	Yield (%)	dr *anti:syn*	ee[a] (%) *anti*	ee[b] (%) *syn*	Yield (%)	dr *anti:syn*	ee[a] (%) *anti*	ee[b] (%) *syn*
2a/Cu(OAc)$_2$	99	1.0:4.0	90	92	96	1.0:4.3	88	93
2b/Cu(OAc)$_2$	69	1.0:4.3	−52	−77	71	1.0:4.3	−58	−80
2a/CuCl$_2$/TEA	99	1.0:4.0	73	93	99	1.0:4.0	68	90
2b/CuCl$_2$/TEA	35	1.0:3.1	−54	−72	39	1.0:3.1	−57	−71
4a/Cu(OAc)$_2$	86	1.0:4.0	84	92	99	1.0:4.0	83	92
4b/Cu(OAc)$_2$	64	1.0:4.0	−84	−92	66	1.0:4.0	−84	−92
11a	99	1.0:4.0	85	92	99	1.0:4.0	84	91
11b	99	1.0:4.1	−83	−92	99	1.0:4.1	−83	−92
***trans*-L*1/Cu(OAc)$_2$**	84	1.0:3.0	76	87	80	1.0:3.0	77	86
***cis*-L*1/Cu(OAc)$_2$**	94	1.0:2.5	−50	−80	96	1.0:3.0	−50	−82
L*2/Cu(OAc)$_2$	75	1.1:1.0	−86	−79	72	1.0:1.0	−86	−83
L*3/Cu(OAc)$_2$	45	1.2:1.0	−47	−18	61	1.0:1.0	−26	−10
L*3/CuCl$_2$/TEA	80	2.6:1.0	−81	−68	90	1.9:1.0	−66	−45
L*4/Cu(OAc)$_2$	72	1.1:1.0	89	90	64	1.1:1.0	89	88

[a] *The ee for anti-diastereomer is expressed as (2S,3R) – (2R,3S)*
[b] *The ee for syn-diastereomer is expressed as (2R,3R) – (2S,3S)*

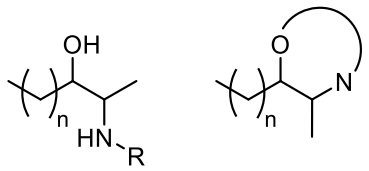
The time dependence of conversion on reaction time was also studied for the reaction of decanal with nitroethane catalysed by the heterogeneous catalyst **11a**. It was found out, that a high yield (>90 %) can be achieved only in four days. This fact enables the execution of enough consecutive catalytic cycles with small amount of catalyst **11a** or **11b** in acceptable time to prepare the 2-nitroalcohols **14** and **15** in sufficiently quantity for subsequent chemical transformations. It was determined that the values of ee achieved in the individual catalytic cycles by the catalysts **11a** and **11b** were mutually comparable and did not decrease even after tenfold recycling.

The 2-nitroalcohols **14** and **15** were prepared as diastereomeric mixture with *syn*-isomer in excess (*anti*/*syn* 1.0/4.0). Unfavourable ratio of *anti*/*syn* diastereomers in the 2-nitroalcohols **14** and **15** (ca. 1.0/4.0) prepared by this experimental protocol could be changed by base-catalysed epimerization at C2 carbon atom (**Scheme 4**), due to the presence of nitro group at this position. Three nitrogen compounds differing in basicity were tested for this epimerization. While pyridine did not affected epimerization even in 10 days (r.t.; MeOH), the use of stronger base TEA led to the mixture of both epimers (1.0/1.0) in a few hours. Unfortunately, the epimerization process was accompanied with partial decomposition of a 2-nitroalcohol to produce starting aldehyde (ca. 10%) in this case. Weaker base, 1,4-dimethylpiperazine, needed approx. 3 days for induction of equilibrium state of both epimers but the decomposition of a 2-nitroalcohol practically did not proceed (presence of aldehyde found was up to 2%). The ee in the 2-nitroalcohols **14** and **15** after epimerization were determined. The initial values of 84% ee for *anti* and 92% ee for *syn* (dr ca. 1.0/4.0) in both 2-nitroalcohols turned to 90% ee for *anti* and 90% ee for *syn* (dr ca. 1.0/1.1). Nevertheless, the separation of individual diastereomers of the 2-nitroalcohols **14** and **15** was impossible probably due to the presence of highly flexible long-chain alkyl group in their structures.



Scheme 4. The epimerization of the 2-nitroalcohols **14** and **15** obtained within eleven catalytic cycles of Henry reaction catalysed by the polymers **11a-b**

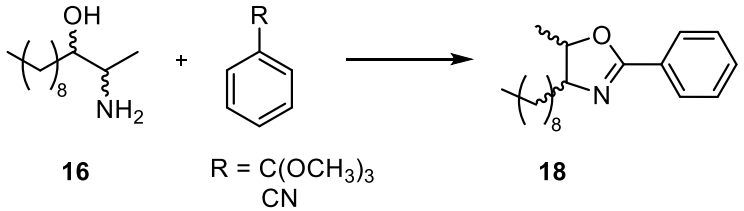
Further, the 2-nitroalcohols **14** and **15** were reduced into the 2-aminoalcohols **16** and **17** *via* catalytic hydrogenation in quantitative yields. In this stage, the efficient method for separation of diastereomers based on suitable modification of vicinal aminoalcoholic moiety was studied. The possible modification of the structure of the 2-aminoalcohols **16** and **17** included an introduction of usual amine protecting group or an acylation. Beside this, it was also considered the conversion of the 2-aminoalcohols **16** and **17** to a O,N-heterocycle (**Scheme 5**), because the cyclic structure represents more rigid system enabling utilization of a standard separation technique.



Scheme 5. General approach in modification of 2-aminoalcohols **16-17** for study of separation of their individual diastereomers

As the most convenient derivatization of **16** and **17** were found a transformation into corresponding 2-phenyloxazoline derivatives **18** and **19**, whose *syn*/*anti* forms can be efficiently separated by simple chromatography (SiO_2; *n*-hexane/AcOEt 3/1; *anti*-isomer R_f = 0.42, *cis*-isomer R_f = 0.31). In the first attempt, where the 2-phenyloxazoline derivative **19** was prepared by treatment of (trimethoxymethyl)benzene to 2-aminododecan-3-ol (**17**) in the presence of acid catalyst TsOH, very low chemical yield (11 %) was achieved. For this reason, the optimization of the reaction conditions for preparation of the 2-phenyloxazoline **18**−**19** was performed. **Table 10** summarizes the results of this optimization study. The reactions of (trimethoxymethyl)benzene with the 2-aminoalcohol **16** did not provide satisfactory yields of **18** in any tested reaction conditions, which differed in reaction time, temperature, amount and type of a catalyst. On the other hand, the condensation reaction of the 2-aminoalcohol **16** with benzonitrile catalysed by anhydrous $ZnCl_2$ (3 eqv.) gave the 2-phenyloxazoline **(±)-*anti*/*syn*-18** in high yield (83%).

Table 10. The performed attempts of synthesis of 2-phenyloxazoline **18** under various reaction conditions.



Entry	Reagent	Solvent	Catalyst (equiv.)	Reaction time (h)	Temperature (°C)	Yield (%)
1	**Ph−C(OCH₃)₃**	MeCN	TsOH (0.1)	10	90	11
2	**Ph−C(OCH₃)₃**	DME	TsOH (0.1)	24	100	20
3	**Ph−C(OCH₃)₃**	DME	TsOH (1)	24	100	33
4	**Ph−CN**	Ph−Cl	$ZnCl_2$ (0.1)	48	140	45
5	**Ph−CN**	Ph−Cl	$ZnCl_2$ (3)	48	140	83

Finally, the prepared 2-phenyloxazolines **18** and **19** were hydrolysed by treatment with 6M HCl in EtOH at 90 °C for 72 h, affording the 2-aminoalcohols **16** and **17** in high yields (80–97 %). The traces of corresponding *N*-benzoyl aminoalcohols (3−10 %) were found in crude products. These impurities can be easily separated by extraction in aqueous citric acid solution/diethyl ether system. Although polymerization of 2-phenyloxazoline derivatives in acidic media *via* CROP process is described in

literature,[25] especially in case of non-substituted derivatives at position 5- of oxazoline cycle,[26] here, this undesirable reaction did not occur, due to the presence of alkyl groups at positions 4- and 5- of oxazoline ring. The characterization data of known stereomers of 2-aminoalcohols **16** and **17** (i.e., **(2*R*,3*S*)-16**, **(2*S*,3*R*)-16**, **(2*S*,3*R*)-17** and **(2*S*,3*S*)-17**) were in good accordance with those found previously in literature.[27,28]

The cytotoxic activity of the stereomers of Clavaminol A and Xestoaminol C (the compounds **16** and **17**) was tested in the selected four cancer cell lines – the suspension Jurkat cell line (human leukemic T cells) and adherent cell lines SH-SY5Y (human neuroblastoma cells), A549 (human carcinoma epithelial cell line) and MG-63 (human osteoblast cells). After 24 h of treatment with tested compounds, it was detected the decrease of intracellular dehydrogenase activity using the WST-1 test in all compounds at concentrations ≤ 80 μmol/L. According to calculated IC_{50} values (**Table 11**), it was found the essential differences in detected antiproliferative activity relating to a type of 2-aminoalcohol **16** or **17** and type of diastereomer (*anti*/*syn*).

Table 11. Evaluation of cytotoxic effects of the stereomers of Clavaminol A and the stereomers of Xestoaminol C.

Compounds	Cell lines (IC_{50}, μmol/l)[a]			
	SH-SY5Y	**Jurkat**	**A549**	**MG-63**
(2*R*,3*R*)-16	63 ± 2	25 ± 2	53 ± 10	29 ± 3
(2*S*,3*R*)-16	81 ± 2	55 ± 10	70 ± 10	32 ± 6
(2*S*,3*S*)-16	60 ± 2	27 ± 2	45 ± 3	22 ± 3
(2*R*,3*S*)-16	70 ± 3	34 ± 4	69 ± 9	37 ± 3
(2*R*,3*R*)-17	21 ± 2	13 ± 1	29 ± 2	12 ± 1
(2*S*,3*R*)-17	53 ± 3	44 ± 13	54 ± 11	22 ± 3
(2*S*,3*S*)-17	22 ± 4	14 ± 1	23 ± 2	12 ± 1
(2*R*,3*S*)-17	42 ± 2	53 ± 10	51 ± 9	24 ± 4

[a] *The results are expressed as IC_{50} ± SD after 24 h treatment*

The results showed that Jurkat and MG-63 cells were more susceptible to cytotoxic effects of stereomers of Clavaminol A and stereomers of Xestoaminol C in comparison to treatment with appropriate stereomers in SH-SY5Y and A549 cells. Another outcome of these experiments was that the stereomers of Xestoaminol C are more potent inhibitors of cell proliferation in comparison to equivalent stereomers of Clavaminol A in all cell lines. Finally, diastereomers with *syn*-configuration, i.e. **(2*R*,3*R*)-16** resp. **(2*S*,3*S*)-16** and **(2*R*,3*R*)-17** resp. **(2*S*,3*S*)-17**, exhibited larger toxic effects in comparison with respective diastereomers with *anti*-configuration, i.e. **(2*R*,3*S*)-16** resp. **(2*S*,3*R*)-16** and **(2*R*,3*S*)-17** resp. **(2*S*,3*R*)-17** (**Table 11**). That finding was proved in all tested cell lines and the differences were especially obvious in Xestoaminol C treated cells.

Interestingly, all selected couples of enantiomeric pairs possessed similar cytotoxic activities in almost all cases. In general, cytotoxic effect of tested compounds depended

significantly on their relative configuration. Nevertheless, the absolute configuration of diastereomers did not affect cytotoxicity significantly. This finding could be helpful for following induction of cytotoxicity using racemic forms which can induce similar toxic effect at concentrations comparable to individual enantiomers. The racemic forms **(±)-*anti*-16** resp. **(±)-*syn*-16,** and **(±)-*anti*-17** resp. **(±)-*syn*-17** can be prepared more easily and with lower costs demand than any enantiomerically pure forms (e.g. naturally occurring Clavaminol A (**(2*R*,3*S*)-16**) and Xestoaminol C (**(2*S*,3*R*)-17**)). Hence, those racemic forms of their stereomers could possess useful potential in anticancer drug development than in the case of individual enantiomers.

4. Conclusion

In this dissertation, the new series of chiral ligands based on 2-(pyridine-2-yl)imidazolidine-4-thione derivatives were prepared. The corresponding copper(II) complex of (2*R*,5*S*)-5-isopropyl-5-methyl-2-(pyridine-2-yl)imidazolidine-4-thione (**3a**) exhibited high enantioselectivity in asymmetric Henry reactions (89–97% ee) whereas the copper(II) complex of (2*S*,5*S*)-5-isopropyl-5-methyl-2-(pyridine-2-yl)imidazolidine-4-thione (**3b**) was less enantioselective (64–83% ee). The modification of the ligands **3a-b** by the introduction of benzyl groups on sulphur atom afforded ligands **5a-b**, whose copper(II) complexes gave higher catalytic activity in the Henry reaction. Moreover, the copper(II) complex of the (2*S*,5*S*)-isomer **5b** provides 2-nitroalcohols with higher enantiomeric purity (89–98 % ee) in comparison with the analogous copper(II) complex of the (2*S*,5*S*)-isomer **3b**.

Further, the heterogeneous catalysts **11a-b** and **12a-b** were prepared by anchoring of (2*R*,5*S*)- (**2a**) and (2*S*,5*S*)-5-isopropyl-2,5-dimethyl-2-(pyridine-2-yl)imidazolidine-4-thione (**2b**) into swellable chloromethylated Merrifield™ resin and JandaJel™ resin to give modified polymers **7a-b** and **8a-b** and subsequent reaction of **7a-b** and **8a-b** with copper(II) acetate. Their catalytic activity and enatioselectivity was practically same as in the case of the previously prepared analogous polymers **10a-b**. They exhibited high enantioselectivity in the asymmetric Henry reaction (~90 % ee). Moreover, their catalytic activity was significant higher in comparison with the homogeneous variant of the catalysts **2a-b/Cu(OAc)$_2$** resp. **4a-b/Cu(OAc)$_2$**. These heterogeneous catalysts can be recycled more than ten times without any decrease in the enantioselectivity. Thus, their application can be considered as more advantageous not only due to economic reasons, but they also represent more environment-friendly variant of catalyst than the homogeneous forms.

The catalytic activity and enantioselectivity of the catalysts **13a-b** prepared by anchoring of the corresponding ligands **3a-b** into swellable chloromethylated Merrifield™ resin an subsequent coordination of copper(II) acetate was also studied. These immobilized complexes (the heterogeneous catalysts) **13a-b** were tested in the asymmetric Henry reaction. They exhibited high catalytic activity and can be easily recycled. Unfortunately, their enantioselectivity was only moderate (~50% ee) probably due to their lower stability in the reaction media. Therefore, these polymers **13a-b** cannot be considered as useful recyclable catalysts for the asymmetric Henry reaction.

Further, the concise synthesis of the natural sphingoid bases Clavaminol A (**(2*R*,3*S*)-16**) and Xestoaminol C (**(2*S*,3*R*)-17**)) and their corresponding stereomers in high enantiomeric purity (ca. 95 % of major enantiomer) was firstly described. The key step of the synthesis represents the asymmetric Henry reaction catalysed with highly efficient catalysts based on copper(II) complexes of different chiral ligands. The diastereomers of target compounds were separated by column chromatography after transformation of their vicinal aminoalcoholic moiety into 2-phenyloxazoline derivatives **18** and **19**.
The individual stereomers of both compounds **16** and **17** were tested for cytotoxic activity in four cancer cell lines (A-549; Jurkat; SH-SY5Y, MG-63) after 24 h. The structure-related differences occurring in all four stereomers of both Clavaminol A and Xestoaminol C were firstly described. According to obtained IC_{50} values, it was observed, that Xestoaminol C stereomers possessed higher cytotoxicity than Clavaminol A stereomers. In addition, it was found that the stereomers with *syn*-configuration, i.e. (2*R*,3*R*)- and (2*S*,3*S*)- isomers of **16** and/or **17**, exhibited stronger cytotoxic effects in comparison with the stereomers having *anti*-configuration, i.e. (2*S*,3*R*)- and (2*R*,3*S*)-isomers of **16** and/or **17**. On the other hand, the individual opposite enantiomers exhibited similar values of IC_{50}. Hence, the important outcome of this study is that racemic forms of tested compounds might be considered as promising targets in pharmaceutical research on the antiproliferative therapy regarding their simpler synthetic availability contrary to preparation of pure enantiomers.

5. List of references

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6. List of Student´s Published Works

- **Articles in impacted journals**

Nováková, G.; Drabina, P.; Frumarová, B.; Sedlák. M. Recyclable Enantioselective Catalysts Based on Copper(II) Complexes of 2-(Pyridine-2-yl)imidazolidine-4-thione: Their Application in Asymmetric Henry Reactions. *Adv. Synth. Catal*. **2016**, *358* (15), 2541–2552.
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Nováková, G.; Drabina, P.; Svoboda, J.; Sedlák. M. Copper(II) complexes of 2-(pyridine-2-yl)imidazolidine-4-thione derivatives for asymmetric Henry reactions. *Tetrahedron: Asymmetry*, **2017**, *28* (6), 791–796.

- **Presented lectures**

G. Nováková, P. Drabina, M. Sedlák: Měďnaté komplexy 2-(pyridin-2-yl)imidazolidin-4-thionů jako enantioselektivní katalyzátory pro Henryho reakci, 69. Zjazd chemikov, Vysoké Tatry, 11. – 15. 9. 2017.

- **Presented posters**

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