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Preparation and application of chiral monotosylated 1,2-diamines in asymmetric synthesis

SUMMARY OF PROFESSIONAL ACCOMPLISHMENTS
SUBMITTED FOR THE HABILITATION PROCEDURE

Warsaw, 22.10.2018

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1. Name and Surname

Piotr Roszkowski

2. Scientific diploma and degrees

Ph.D. degree in chemistry – University of Warsaw, Faculty of Chemistry, Poland, 2007, title of the Ph. D. thesis: „Stereoselective synthesis of tetrahydro-β-carboline and tetrahyroiso-quinoline systems using amines and their derivatives as chiral inducers"; supervisor: Professor Zbigniew Czarnocki.

M. Sc. degree in chemistry - Siedlce University of Natural Sciences and Humanities (previously Podlasie Academy), Department of Chemistry, Poland, 2001, title of the M. Sc. thesis: „Syntehsis and mesomorphic properties of mesogens from the nOSCl series"; supervisor: Ph. D. Mirosława Ossowska-Chruściel.

3. History of employment

Adjunct – University of Warsaw, Faculty of Chemistry, 2011- presently;

Short-term postdoctoral internship - Montanuniversität Leoben, Lehrstuhl für Chemie der Kunststoffein in Leoben (Austria), 01st of July-30th of September 2016, member of the project.

Assistant – University of Warsaw, Faculty of Chemistry, 2009- 2011;

Independent scientific and technical employee – University of Warsaw, Faculty of Chemistry, 2006-2009.

4. Indication of achievement resulting from Article 16 Section 2 of the Act on University Degrees and the University Title and on University Degrees and the University Title in the Field of Fine Arts of March 14, 2003 (Journal of Laws No. 65, item 595, with later amendments):

a) Title of scientific achievement

Preparation and application of chiral monotosylated 1,2-diamines in asymmetric synthesis

b) List of publications constituting the scientific achievement;

The scientometric data taken from Webof Science at 22nd of September 2018;
* corresponding author; †IF – impact factor of the journal according to the year of publication

H1. P. Roszkowski, J. K. Maurin, Z. Czarnocki*,

„First enantioselective synthesis of aptazepine”,

Synthesis **2012**, 44, 241-246, IF = 2.722 (IF = 2.500†), number of citations = 4.

My contribution to this work concerns: the determination of the scientific goal, design and carrying out of the multi-step synthesis of aptazepine, the optimization of individual synthetic steps, obtaining and purification of an intermediates and the final compound, collection and interpretation of experimental results and preparation of the manuscript for publication. I estimate my contribution to be equal to 75%.

H2. P. Roszkowski, J. K. Maurin, Z. Czarnocki*,

„Novel (*R*)-(+)-limonene-derived ligands: Synthesis and application in asymmetric transfer hydrogenations”,

Tetrahedron: Asymmetry **2012**, 23, 1106-1110, IF = 2.126 (IF = 2.115†), number of citations = 6.

My contribution to this work concerns: design and synthesis of ligands, the optimization of individual synthetic steps, obtaining and purification of the chiral ligands, carrying out of the model reduction reactions using ruthenium complexes modified with previously obtained diamines, collection and interpretation of experimental results and preparation of the manuscript for publication. I estimate my contribution to be equal to 70%.

H3. P. Roszkowski*, J. K. Maurin, Z. Czarnocki,

„ Synthesis of new mono-*N*-tosylated diamine ligands based on (*R*)-(+)-limonene and their application in asymmetric transfer hydrogenation of ketones and imines”,

Tetrahedron: Asymmetry **2013**, 24, 643-650, IF = 2.126 (IF = 2.165†), number of citations = 22.

My contribution to this work concerns: the partially determination of the scientific goal, design and synthesis of ligands, the optimization of individual synthetic steps, obtaining and purification of the chiral ligands, carrying out of the model reduction reactions using ruthenium complexes modified with previously obtained diamines, collection and interpretation of experimental results and preparation of the manuscript for publication. I estimate my contribution to be equal to 80%.

H4. **P. Roszkowski***, P. Małecki, J. K. Maurin, Z. Czarnocki,

„ Novel (+)-3-carene derivatives and their application in asymmetric synthesis”,

Synthesis **2015**, 47, 569-574, IF = 2.722 (IF = 2.652†), number of citations = 3.

My contribution to this work concerns: design and partially synthesis of ligands, the optimization of individual synthetic steps, obtaining and purification of the chiral ligands, carrying out of the model reduction reactions using ruthenium complexes modified with previously obtained diamines, collection and interpretation of experimental results and preparation of the manuscript for publication. I estimate my contribution to be equal to 60%.

H5. P. Roszkowski*, J. K. Maurin, Z. Czarnocki,

„ The enantioselective synthesis of (*S*)-(+)-mianserin and (*S*)-(+)-epinastine”,

Beilstein J. Org. Chem. **2015**, 11, 1509-1513, IF = 2.330 (IF = 2.697[†]), number of citations = 1.

My contribution to this work concerns: the determination of the scientific goal, design and carrying out of the multi-step synthesis of mianserin and epinastine, the optimization of individual synthetic steps, obtaining and purification of an intermediates and the final compounds, collection and interpretation of experimental results and preparation of the manuscript for publication. I estimate my contribution to be equal to 80%.

H6. P. Roszkowski*, J. K. Maurin, Z. Czarnocki,

„New *N*,*N*-diamine ligands derived from (-)-menthol and their application in the asymmetric transfer hydrogenation”,

Tetrahedron: Asymmetry **2017**, 28, 532-538, IF = 2.126 (IF = 2.126[†]), number of citations = 2.

My contribution to this work concerns: the determination of the scientific goal, design and synthesis of ligands, the optimization of individual synthetic steps, obtaining and purification of the chiral ligands, carrying out of the model reduction reactions using ruthenium complexes modified with previously obtained diamines, collection and interpretation of experimental results and preparation of the manuscript for publication. I estimate my contribution to be equal to 80%.

H7. P. Roszkowski*, J. K. Maurin Z. Czarnocki,

„(-)-Menthol as a source of new *N*,*N*-diamine ligands for asymmetric transfer hydrogenation”,

Tetrahedron Lett. **2018**, 59, 2184-2188, IF = 2.125 (IF = 2.125[†]), number of citations = 0.

My contribution to this work concerns: the determination of the scientific goal, design and synthesis of ligands, the optimization of individual synthetic steps, obtaining and purification of the chiral ligands, carrying out of the model reduction reactions using ruthenium complexes modified with previously obtained diamines, collection and interpretation of experimental results and preparation of the manuscript for publication. I estimate my contribution to be equal to 80%.

c) Description of the scientific goal and the results described in the publications constituting scientific achievement

The scientific goal of the publication cycle, which is the basis of the achievement presented in this dissertation, was the synthesis of new monotosylated 1,2-diamine derivatives structurally referring to the frame of *trans*-1,2-diaminocyclohexane, as well as the use of known and newly obtained 1,2-diamines as chiral inductors in selected types of asymmetric transformations. I have put an emphasis on the use of 1,2-diamines in the construction of

chiral ruthenium complexes and their use in enantioselective reduction of C=O and C=N double bonds.

The research presented in this dissertation is the basis of a cycle of seven thematically related publications (**H1**-**H7**) and constitute the basis of the scientific achievement. Within the field of study, two closely related research areas can be distinguished:

1. The synthesis of new chiral monotosylated *trans*-1,2-diamines structurally related to *trans*-1,2-diaminocyclohexane based on natural monoterpenes, and their use as ligands for the construction of ruthenium complexes (publications **H2**, **H3**, **H4**, **H6** and **H7**).
2. The use of the asymmetric hydrogen transfer reaction catalyzed with chiral ruthenium complexes, obtained on the basis of monotosylated *trans*-1,2-diamines, for the enantioselective synthesis of aptazepine, mianserin and epinastine (publications **H1** and **H5**).

Introduction

Compounds which contain the chiral 1,2-diamine structural motif in their structure occur in nature and are also used in many types of asymmetric transformations. The 1,2-diamine system is present in many natural products and their derivatives, and is often responsible for their biological activity.[1] An example of natural molecules in which we can find a diamine motif is biotin (vitamin H, **1**), which is a coenzyme of carboxylase and same well-known antibiotics from the group of penicillins **2** and cephalosporins **3** (Figure 1). Also many synthetic derivatives, that have 1,2-diamines- subunits, exhibit a wide spectrum of biological activities. The best example is oxaliplatin **4**, a cytostatic used to treat cancer, mainly colon cancer.

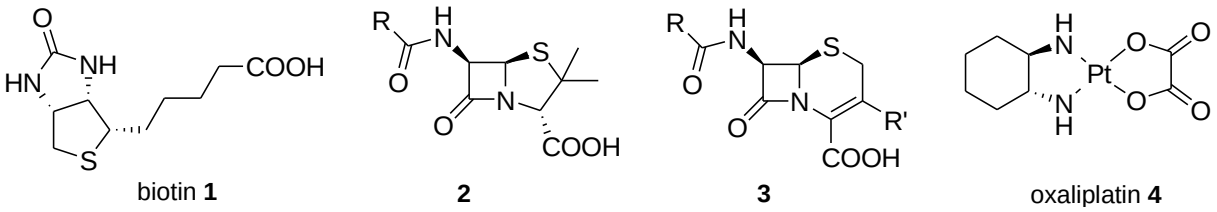
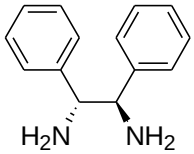
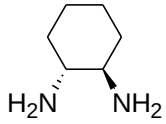


Figure 1. Examples of biologically active compounds containing a 1,2-diamine system.

The optically pure 1,2-diamines and their derivatives are often applied as chiral inductors in stereoselective synthesis.[3,4] Among many compounds of this class, the *trans*-1,2-diphenylethylenediamine (DPEN) **5** and *trans*-1,2-diaminocyclohexane (CYDN, DACH) **6** are the most frequently used (Fig. 2). For example, they have been used for the separation of chiral aldehydes, by the formation of diastereomeric aminals.[3] The derivatives of these amines, appropriate phosphonamides, have been successfully applied as chiral auxiliaries in the synthesis of optically active α-alkyl phosphonic acids or the asymmetric olefination of cyclohexanones in the Wittig reaction. In the group of Prof. Gawroński, DACH has been used as a building block for the construction of a broad range of chiral macrocycle structures, like trianglimines, rhombimines and calixsalens.[5-7]



5
DPEN



6
CYDN, DACH

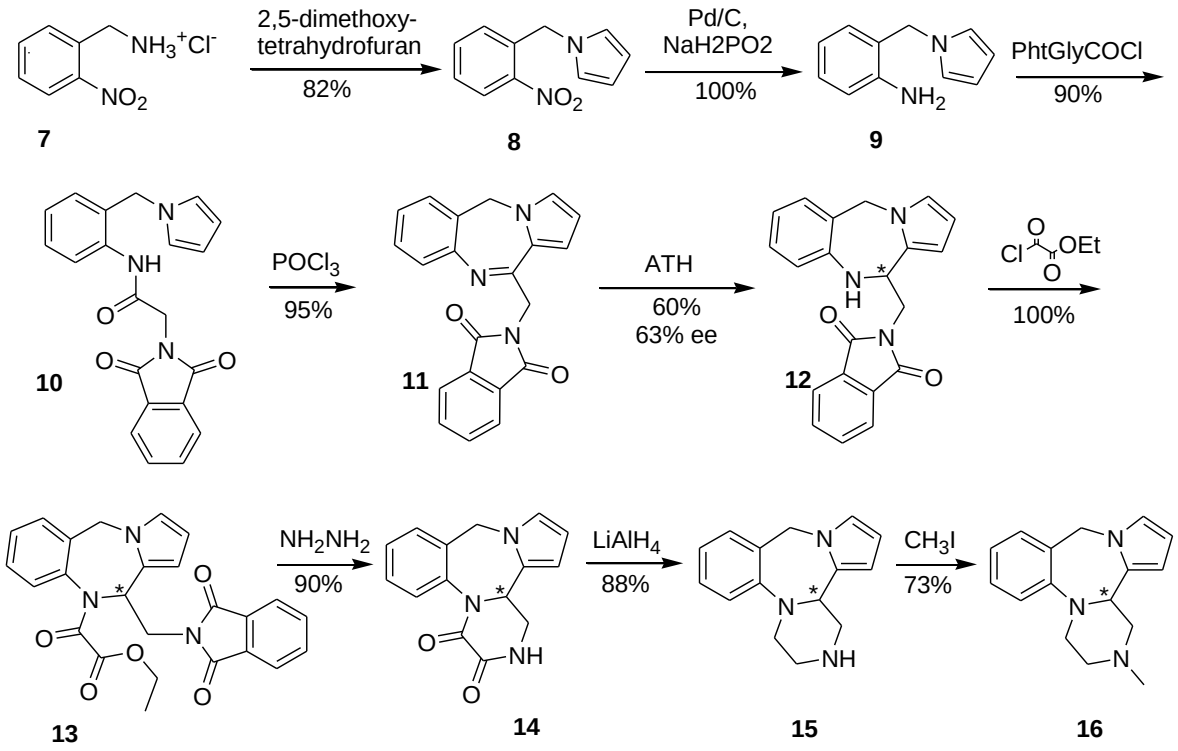
Figure 2. The structures of the most popular compounds with 1,2-diamine system.

Trans-1,2-diaminocyclohexane and its derivatives are widely used in asymmetric synthesis as ligands, organocatalysts and chiral auxiliaries.[4,8] Using this amine, Jacobsen and Katsuki developed the chiral salene complexes of manganese (III) and used them in the asymmetric epoxidation of *Z*-alkenes.[9,10] Other chromium (III) salen complexes and copper (II) salan type compounds have found application in enantioselective nitroaldol reactions.[11,12] In turn, the thiourea and carbamate derivatives of 1,2-diaminocyclohexane are efficient organocatalysts of Michael and Strecker reactions as well as for the addition of aryl ketones to nitroalkenes.[13-15] Among the many applications of DACH derivatives, it is important to use them as ligands for the construction of chiral transition metal complexes (ruthenium, rhodium and iridium) to the enantioselective reduction of C=O and C=N double bonds in the conditions of asymmetric hydrogen transfer reaction (ATH).[16-18] The dynamic development of this method of hydrogenation of double bonds is linked to the use of monotosylated 1,2-diamines as chiral inducers and was initiated by R. Noyori in 1995.[19-20] In this reduction method, a suitable alcohols (mainly isopropanol) or formic acid (in the form of an azeotropic mixture with triethylamine) are used as hydrogen donors instead of a molecular hydrogen. Currently used catalysts are based mainly on P,P, P,N, N,N and N,O ligands and show high activity in the model hydrogenation reactions of C=O and C=N bonds.[21-23]. One of the most effective complexes in this method of reduction are complexes of monotosylated diamines **5** and **6** or their derivatives. Unfortunately, the known complexes are less effective in the reduction of more sterically hindered molecules. An adaptation of a suitable catalyst to a specific molecular target requires extensive screening in a group of commercially available catalytic systems, and this does not often give the intended results. Therefore, there is a need to search new ligands or modify of the structure of the best known ligands, to create more compatible complexes. Importantly, the formation of new ligands/complexes should lead to cheaper equivalents with comparable or better catalytic properties.

In the studies carried out in this dissertation, I wanted to study the effect of the alkyl substituents in the *trans*-1,2-diaminocyclohexane ring on the activity of ruthenium complexes in the enantioselective reduction of C=O and C=N double bonds. I decided that the simplest way to introduce such substituents will be the usage of chiral building blocks such as natural monoterpenes.

A discussion of the test results presented in publications H1-H7

Bearing in mind the potential of asymmetric hydrogen transfer reaction and my previous experience in the reduction of C=N endocyclic bonds,[21-23] I decided to use this method in the enantioselective synthesis of aptazepine, a compound with antidepressant properties. Aptazepine is structurally closely related to two other active substances: mianserin and mitrazapine, which are used to treat depression. Unfortunately, they occur in drugs as a racemic mixtures, despite the therapeutic activity resulting mainly from one of the enantiomers. Designing and realizing the stereoselective synthetic pathway of aptazepine, I treated it as a testing ground for further research focused on the enantioselective synthesis of mianserin and mitrazapine. The research undertaken as a part of this project is the subject of publication **H1**. In Scheme 1, the sequence of reactions leading to aptazepine in an enantiomerically pure form was presented.



Schem1 1. The enantioselective synthesis of aptazepine.

I started the synthesis using cheap and commercially available substrates: 2-nitrobenzylamine hydrochloride and 2,5-dimethoxytetrahydrofuran. In the cyclization reaction of amide **10** using the Bischler-Napieralski method, I obtained a prochiral imine **11** with high 95% yield. The key step of the synthetic pathway was the introduction of a stereogenic center to the molecule that I intended to implement by the enantioselective reduction of the prochiral imine under the asymmetric transfer hydogenation conditions. For this purpose, I synthesized the previously described ruthenium complexes **17-21** (Figure 3) and used them in the stereoselective reduction of C=N double bond.

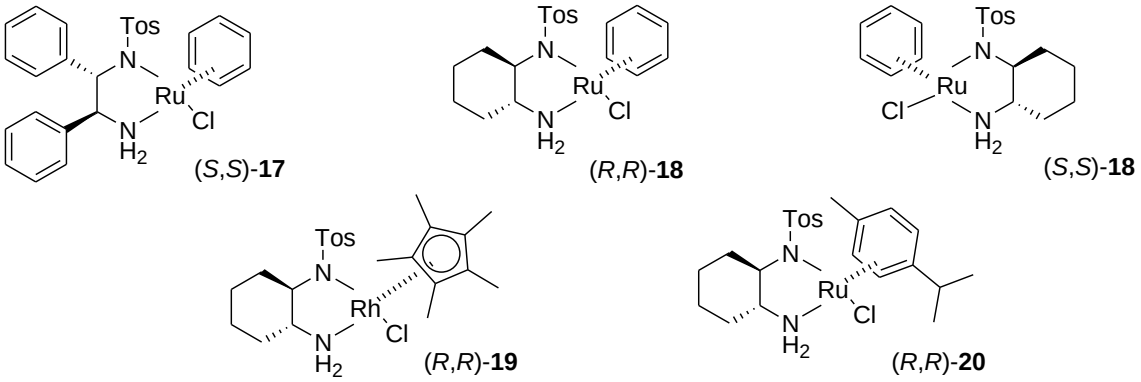


Figure 3. The structures of chiral catalysts used in asymmetric reduction of imine **11**.

As I have shown in Table 1, the hydrogenation reaction with the help of ruthenium catalyst **18** gave a chiral amine with a good yield and moderately high asymmetric induction. The unreacted substrate was recovered after the reaction and reduced again, which allowed to achieve 90% process yield. In turn, the Ru-**17** complex was less active and led to the amine **12** with a 38% enantiomeric excess. More sterically hindered ruthenium **20** and rhodium **19** complexes have been found to be essentially inactive in the reduction of this imine. Although I obtained the amine **12** with an enantiomeric excess of 63%, it was effectively transformed into the enantiopure form upon one recrystallization. The optical purity was confirmed by HPLC using a column with chiral stationary phase (Chiralcel OD-H). The absolute configuration of the obtained amine was confirmed by X-ray analysis, which allowed to conclude, that the complex with the (*S*,*S*)-**18** configuration gives the product (*S*)-**12**.

Table 1. The results of asymmetric hydrogenation of imine **11**.

Imine	Cat.	S/C substrate/cat.	Solvent	Time (h)	Yield.[a] ( )[b] (%)	ee (%)
11	(*S*,*S*)-**17**	51	CH_3CN	72	31 (91)	38 (*S*)
11	(*S*,*S*)-**17**	54	CH_2Cl_2	96	51(89)	27 (*S*)
11	(*R*,*R*)-**18**	27	CH_3CN	96	60 (90)	63 (*R*)
11	(*S*,*S*)-**18**	27	CH_3CN	96	58 (86)	61 (*S*)
11	(*R*,*R*)-**18**	26	CH_2Cl_2	96	55 (87)	38 (*R*)
11	(*R*,*R*)-**19**	37	CH_3CN	72	7 (-)	-
11	(*R*,*R*)-**20**	19	CH_3CN	72	1 (-)	-

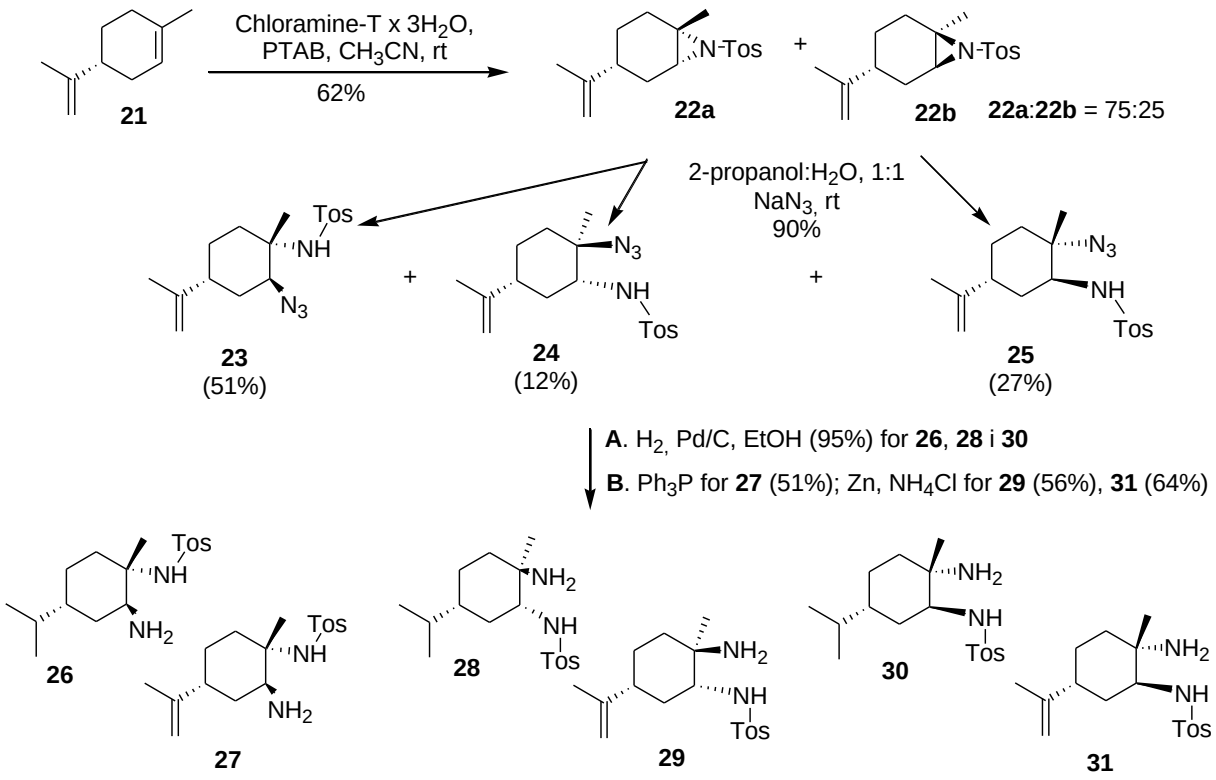
[a] isolated yield; [b] field based on consumer substrate

In the next step, the enantiomerically pure amine **12** in reaction with ethyl oxalyl chloride gave quantitatively amide **13**. Then, I unblocked the amino function using hydrazine, which by intramolecular cyclisation led to the formation of the diketopiperazine ring **14**. I removed the carbonyl groups with lithium aluminum hydride and after methylation of the amino function, I obtained the enantiomerically pure aptazepine **16**.

The enantioselective reduction of imine occurred with a moderately good asymmetric induction, but the primary aim of the hydrogenation was to obtain the product in an optically pure form. Considering the limitations I encountered during the hydrogenation using the most effective *N*,*N* ruthenium complexes, I decided to modify the structure of the 1,2-

diaminocyclohexane ligand by introducing of alkyl substituents therein. I hoped that this approach would give a more active catalyst than those used previously. After analyzing the literature, I found that the easiest way to synthesize such ligands could be to usage of readily available molecules with a defined stereochemistry and susceptible to functionalization to the *trans*-1,2-diamine system. Such a cheap source of chiral molecules can be monoterpenes, which, in diastereoselective be manner, can converted to derivatives containing a diamine moiety on the basis of an already existing stereogenic center in the basic structure.

I began the research in this area from the use of natural (+)-limonene, which was converted into a monosylated 1,2-diamine system in the three-step sequence reactions, as shown in Scheme 2 (publications **H2** and **H3**). In the first stage, I used the method of aziridation of the carbon-carbon double bond proposed by Sharpless[14] and later used for the (+)-carene[15] functionalization. The reaction of limonene with Chloramine-T trihydrate in the presence of phenyltrimethylammonium tribromide (PTAB) gave a mixture of *cis*- and *trans*-aziridinolimonene with a 62% yield, in which the *trans*-isomer was the main product. Based on ^{1}H NMR spectrum, I found that the ratio of both formed isomers is about 75:25.

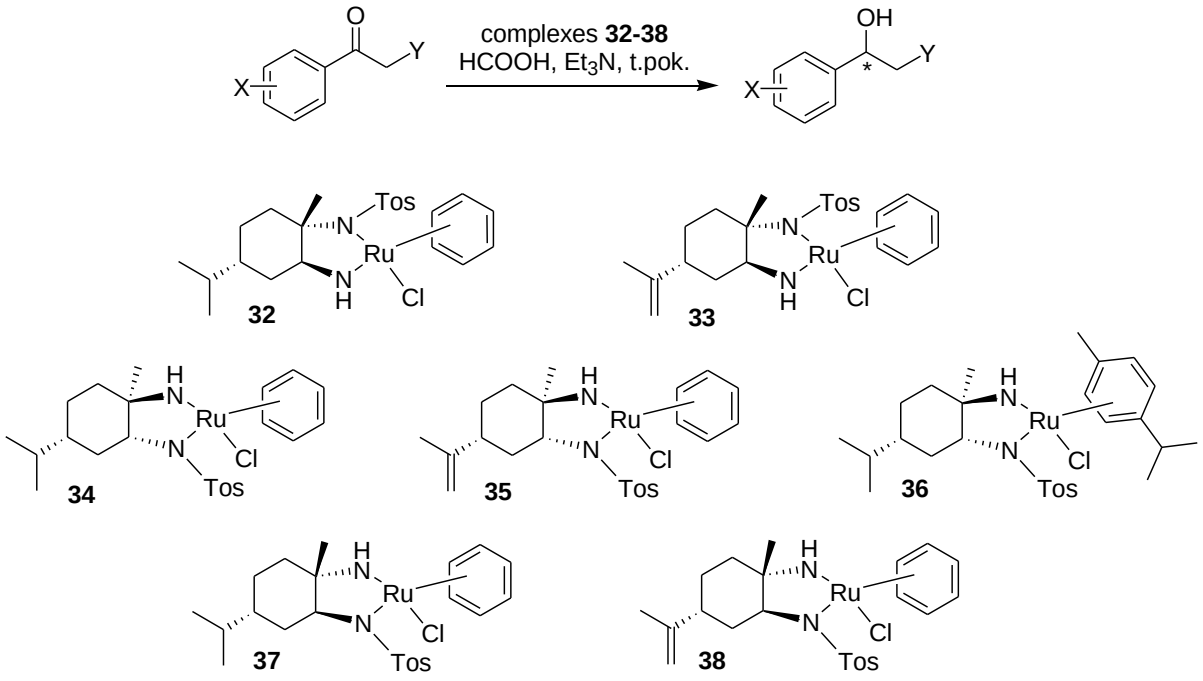


Schemat 2. The synthetic pathway of monotosylated diamines **26-31**.

Then, I opened the *N*-Tosylaziridines ring **22a,b** using sodium azide. The nucleophilic attack of azide ion on *cis*-*N*-tosylaziridines **22b** occurs regio- and diastereoselectively at the more sterically hindered tertiary carbon atom and leads to the isomer 2**5** (27% yield) with the inversion of configuration at this stereogenic centre. Whereas, the nucleophilic attack on *trans*-aziridine **22a** is diastereoselective but not regioselective. As a result of the azide ion attack two regioisomers were obtained- **23** and **24**. The dominant one is azide **23** (51%) formed by the nucleophilic attack of the N_3^- ion at less sterically hindered, secondary carbon

atom C-2. The resulting mixture of azides was separated by column chromatography. The absolute configuration of isolated isomers **23-25** were determined on the basis of an X-ray analysis made in collaboration with prof. Jan Maurin from National Medicines Institute (publications **H2** and **H3**). In the last step, I carried out the reduction of azide group in order to obtain the final monotosylated 1,2-diamine system. The hydrogenation of individual isomers in the presence of Pd/C led to the reduction of both the azide function and the double bond in the isopropylene substituent. I obtained compounds **26**, **28** and **30** with yields above 90%. In order to selectively reduce the azide group, I used the Staudinger method. In this way, I obtained diamine **27** with a yield of 51%. Unfortunately, this method turned out to be inefficient with the case of isomers **24** and **25**. Therefore, I reduced these azides using a mixture of zinc and ammonium chloride, which allowed to obtain amines **29** and **31** with a higher yield than previously.

In order to evaluate amines **26-31** as potential ligands, I chose the Ru- catalyzed asymmetric hydrogen transfer (ATH) protocol on a series of ketones. The appropriate complexes **32-38** were prepared *in situ* by mixing $[RuCl_2(benzene)]_2$ or $[RuCl_2(p\text{-cymene})]_2$ with monotosylated diamines 2**6-31** and triethylamine (Ru:Amine:Et_3N molar ratio = 1:2.5:2) in acetonitrile (Scheme 3). After 20 min. the solution of the catalyst was mixed with appropriate ketone and subsequently, the formic acid/triethylamine azeotropic mixture was added. The reduction of aromatic ketones were carried out at room temperature and the reaction progress was monitored by TLC. The products were isolated by a short-path column chromatography and the enantiomeric excess was determined by GC analysis on a chiral stationary phase. The configuration of the obtained alcohols was determined by a comparison of the sign of the specific rotation with literature data. I summarized the results of the enantioselective reduction of aromatic ketones in Tables 2-3.



Scheme 3. The asymmetric transfer hydrogenation to aromatic ketones using complexes **32-38**.

The collected reduction data show that the rate and the enantioselectivity of the reaction are highly influenced by the structure of the ligands **26**-**31** and η^6-arene part of the complex. The catalytic activity of complex **32** and **33**, in which the methyl and isopropyl/isopropenyl substituents in cyclohexane ring are in a *trans* position, is small under the tested conditions and after 20 days leads to the corresponding alcohols with very weak asymmetric induction 9-36% ee The presence of C=C double bond in the structure of catalyst **33** gave a significant increase in the enantioselectivity of ketones reduction in comparison to its analogue **32** (Table 2), but still remained at a low level.

Table 2. The results of the ATH reductions of aromatic ketones with complexes **32-36**.[a]

Cat.	X	Y	Time (h)	Yield. (%)	ee (%)[b,c]	$[\alpha]_D^{23}$
32	H	H	480	45	9 (*S*)	- 4.8
33	H	H	480	44	17 (*R*)	+ 9.2
32	H	CH_3	480	17	11 (*S*)	- 5.8
33	H	CH_3	480	15	36 (*R*)	+ 19.3
34	H	H	32	100	92 (*R*)	+ 50.1
36	H	H	40	58	75 (*R*)	+ 40.5
35	H	H	42	100	93 (*R*)	+ 50.7
34	H	CH_3	48	100	88 (*R*)	+ 46.9
35	H	CH_3	72	66	90 (*R*)	+ 48.0
34	*o*-Br	H	32	87	25 (*R*)	+ 12.9
35	*o*-Br	H	18	100	14 (*R*)	+ 7.1
34	*m*-Br	H	24	99	80 (*R*)	+ 25.8
35	*m*-Br	H	18	100	82 (*R*)	+ 26.3
34	*p*- Br	H	26	94	82 (*R*)	+ 31.0
35	*p*- Br	H	18	100	81 (*R*)	+ 30.3
34	*o*-CH_3	H	92	30	47 (*R*)	+ 40.1
35	*o*-CH_3	H	52	83	26 (*R*)	+ 22.2
34	*m*-CH_3	H	92	78	76 (*R*)	+ 43.8
35	*m*-CH_3	H	52	100	86 (*R*)	+ 49.2
34	*p*-CH_3	H	92	52	89 (*R*)	+ 52.7
35	*p*-CH_3	H	52	92	91 (*R*)	+ 53.4
34	*o*-Cl	H	96	85	38 (*R*)	+ 27.0
35	*o*-Cl	H	18	100	16 (*R*)	+ 11.0
34	*m*-Cl	H	96	100	79 (*R*)	+ 31.8
35	*m*-Cl	H	18	95	82 (*R*)	+ 32.9
34	*p*-Cl	H	96	96	82 (*R*)	+ 39.4
35	*p*-Cl	H	18	100	87 (*R*)	+ 41.2
34	*p*-OCH_3	H	92	98	83 (*R*)	+ 41.9
35	*p*-OCH_3	H	72	82	88 (*R*)	+ 44.5

I obtained the best results of the reduction of aromatic ketones using catalysts **34** and **35**, in which the amino group is connected to the tertiary carbon atom, and the methyl and isopropyl/ isopropylene substituents in the cyclohexane ring are in a *cis* position. The results collected during the study indicate that this configurations of substituents is optimal for the hydrogenation of ketones under the asymmetric hydrogen transfer conditions. The introduction of a larger *p*-cymene ligand in the catalyst structure **36** resulted in a significant decrease in yield and the enantioselectivity of reaction (Table 2). Only in case of the reduction of *ortho*-substituted ketones, I observed a significant decrease in the stereoselectivity of the process, probably due to unfavorable steric interactions.

Table 3. The results of ATH reductions of aromatic ketones with complexes **37-38**.[a]

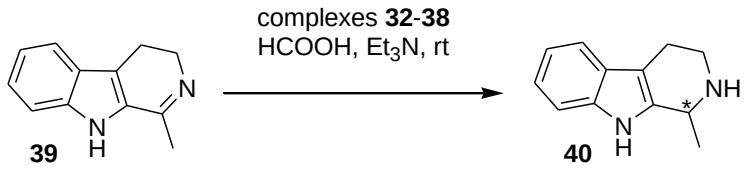
Cat.	X	Y	Time (h)	Yield. (%)	ee (%)[b,c]	$[\alpha]_D^{23}$
37	H	H	96	10	60 (*S*)	- 33.0
38	H	H	96	21	37 (*S*)	- 20.5
37	H	CH_3	96	12	52 (*S*)	- 27.5
38	H	CH_3	96	36	34 (*S*)	- 18.0
37	*o*-Br	H	96	41	32 (*S*)	- 16.7
38	*o*-Br	H	96	37	31 (*S*)	- 15.9
37	*m*-Br	H	96	52	56 (*S*)	- 18.0
38	*m*-Br	H	96	34	50 (*S*)	- 16.1
37	*p*- Br	H	96	82	74 (*S*)	- 28.0
38	*p*- Br	H	96	67	52 (*S*)	- 19.3
37	*m*-CH_3	H	96	24	62 (*S*)	- 35.3
38	*m*-CH_3	H	96	41	51 (*S*)	- 29.4
37	*o*-Cl	H	96	81	15 (*S*)	- 10.2
38	*o*-Cl	H	96	62	20 (*S*)	- 14.2
37	*m*-Cl	H	96	60	81 (*S*)	- 32.8
38	*m*-Cl	H	96	96	62 (*S*)	- 25.0
37	*p*-Cl	H	96	83	67 (*S*)	- 32.3
38	*p*-Cl	H	96	70	47 (*S*)	- 22.4
37	*p*-OCH_3	H	96	16	7 (*S*)	- 3.5
38	*p*-OCH_3	H	96	8	13 (*S*)	- 6.5

[a] The reaction was carried out at room temperature using a ketone (2.40 mmol) in CH_3CN (1mL) and a formic acid-triethylamine mixture (5:2, 1 mL) with S/C = 100; [b] Determined by GC analysis using a Supelco cyclodextrin β-DEX 120 capillary column (20 m x 0.25 mm I.D. and 0.25 μm film thickness); [c] Determined on the basis of the sign of the specific rotation of the isolated product.

The third group of complexes **37** and **38** showed lower values of asymmetric induction than catalysts **14-15** (Table 3). The change of configuration on the carbon atoms connected with amine groups from (*R*,*R*) in **34** and **35** to (*S*,*S*) in **37** and **38** not only resulted in the formation of alcohols of the opposite configuration, but also more importantly, gave products with much lower chemical yield and enantiomeric excess (Table 3). The opposite configuration of carbon

atoms causes the methyl and isopropyl/isopropylene substituents in the cyclohexane ring to be in a *trans* position, and affects the unfavorable spatial structure of the entire complex molecule.

After determining the activity of complexes **32-38** in the enantioselective reduction of aromatic ketones, I decided to use them for asymmetric hydrogenation of endocyclic imines. Initially, the ATH process was studied to reduction of 1-methyl-3,4-dihydro-β-carboline as the model imine (Scheme 4).



Scheme 4. The asymmetric transfer hydrogenation of imine **39** with catalysts **32-38**.

As it might have been expected, I obtained the best results using catalyst **34-35**. Complex **15** possessing a double C=C bond gave amine **39** with excellent results, a 100% yield and a 98% ee (Table 4). Similarly to the reduction of ketones, I also observed a decrease in the activity of complexes **37-38** in relation to **34-35**. Interestingly, the use of non-active complexes **32-33** in this case led to the formation of the product **40** with a quantitative yield and a comparable enantiomeric excess to the catalysts **37-38**.

The promising results of the imine **39** reduction prompted me to test complexes **32-38** on other, more sterically demanding imines and iminium salts depicted in Figure 4. I summarized the results of hydrogenation of imines\iminium salts in Table 4. The asymmetric reduction of imine **12**, using the most active complexes **34-35** gave an appropriate amine with slightly lower enantioselectivity than the Noyori-type catalyst Ru-**18** (publication **H1**). More sterically demanding complex **36** was completely inactive in relation to this imine, and analogs **37-38** led to the racemic amine. In case of imine **41** the results of asymmetric hydrogenation for all complexes **32-38** were comparable and provided the product with quantitative yield but low optical purity (24-34% ee). The hydrogenation of iminium chloride **42** gave the best results in the presence of complex **34** and led to Crispine A with a purity of 84% ee. The less active analogs **32-33** and **37-78** produced a product in a racemic form or with a low enantioselectivity. I observed similar relationships during the reduction of salt **43**, where once again, the complexes **34** (48% ee) and **35** (56% ee) were the most active.

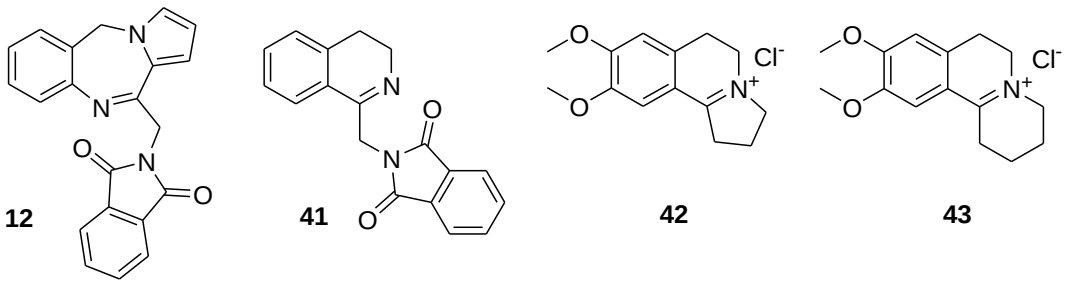


Figure 4. The structure of imines\ iminium salts with to ATH.

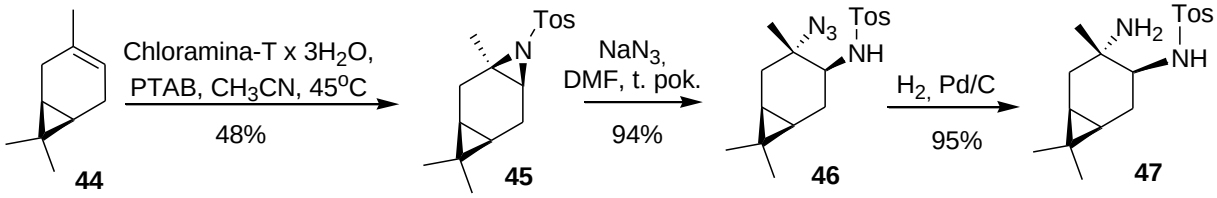
The collected results from the reduction of ketones and imines clearly indicate that the enantioselectivity of the process strongly depends on both the structure of the catalyst and the substrate.

Table 4. The ATH reduction of imines\ iminium salts with catalysts **32-38**.

Cat.	Imine	Time (h)	Yield. (%)	ee (%)[a,b]	$[\alpha]_D^{23}$
32	**39**	20	100	59 (*S*)[c]	- 36.6
33	**39**	20	100	50 (*S*)[c]	- 31.3
34	**39**	20	100	95 (*S*)[c]	- 60.6
35	**39**	20	100	98 (*S*)[c]	- 61.3
37	**39**	20	100	54 (*R*)[c]	+ 33.6
38	**39**	20	100	48 (*R*)[c]	+ 30.2
32	**12**	19	14	19 (*S*)	- 8.1
33	**12**	19	17	22 (*S*)	- 9.4
34	**12**	19	55	47 (*R*)	+ 19.8
35	**12**	19	70	48 (*R*)	+ 20.1
36	**12**	19	0	rac	0
37	**12**	19	32	rac	0
38	**12**	19	47	rac	0
32	**41**	4	100	27 (*R*)	+ 23.0
33	**41**	4	100	24 (*R*)	+ 20.2
34	**41**	1.5	100	33 (*R*)	+ 28.1
35	**41**	1.5	100	25 (*R*)	+ 21.0
36	**41**	5	0	rac	0
37	**41**	4	100	34 (*S*)	- 28.6
38	**41**	4	100	33 (*S*)	- 27.8
32	**42**	16	77	rac	0
33	**42**	16	76	rac	0
34	**42**	5	72	84 (*S*)	- 84.0
35	**42**	5	74	53 (*S*)	- 53.4
36	**42**	16	70	1 (*S*)	- 1.0
37	**42**	8	72	16 (*S*)	- 16.2
38	**42**	8	81	10 (*S*)	- 10.2
32	**43**	16	94	6 (*S*)	- 6.9
33	**43**	16	90	rac	0
34	**43**	5	90	48 (*S*)	- 52.1
35	**43**	5	89	56 (*S*)	- 60.5
36	**43**	16	87	3 (*S*)	-3.0
37	**43**	8	89	31 (*S*)	-34.0
38	**43**	8	90	35 (*S*)	-38.6

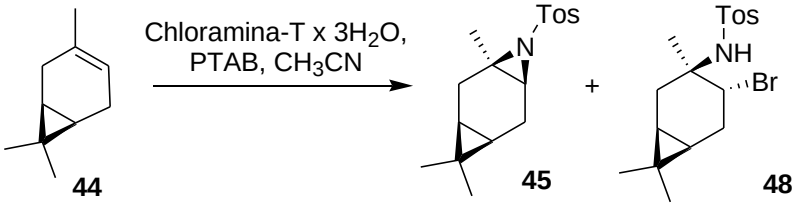
[a,b] Determined by the sign and value of the specific rotation of the isolated product; Determined by HPLC analysis using Daicel OD-H column.

The next target which I realized was the synthesis of the monotosylated 1,2-diamine system based on natural (+)-3-carene (publication **H4**). Taking into consideration the previous experience, I carried out the three-step synthesis as shown in Scheme 4. The reaction of 3-carene with chloramine-T trihydrate and PTAB at 25 ^{o}C gave one isomer of aziridine **45** only with a 34% yield. In this case, the presence of the isopropylidene bridge in the carene molecule is a sufficient barrier for the process to occur diastereoselectively. In addition, I isolated the second compound, which is a bromine derivative **48**.



Scheme 5. The synthetic pathway of monotosylated diamine **47**.

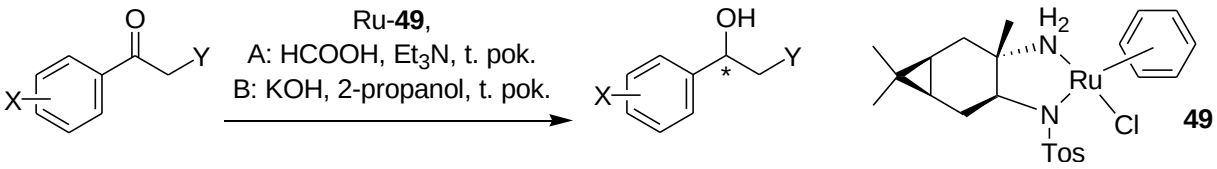
Due to the low efficiency of this reaction I decided to check the influence of temperature. It turned out that increasing the temperature to 45 ^{o}C leads only to the aziridine **45** with a 48% yield, while its reduction to 0 ^{o}C gives, as the main product, the bromine derivative **48** with a 23% yield (Scheme 6). The subsequent nucleophilic ring opening of carene *N*-tosylaziridine **45** by the azide anion is a regio- and diastereoselective process. The reaction of **45** with sodium azide occurred at the more sterically hindered tertiary carbon atom and led to the formation of the azido amine **46** with the inversion of configuration at this stereogenic center. The absolute configurations of compounds **46** and **48** were determined on the basis of X-ray analysis (in collaboration with Prof. Jan K. Maurin). Finally, I hydrogenated the compound **46** over 10% Pd/C and obtained the desired monotosylated diamine **47** almost quantitatively.



Temp. (^{o}C)	Czas (h)	**2** (%)	**5** (%)
0	4	20	23
25	4	34	12
45	4	48	0

Scheme 6. The optimization of aziridination reaction.

As in the case of limonene derivatives, I used amine **47** to build the ruthenium complex **49** and evaluated its activity in the model reactions of asymmetric hydrogen transfer to selected aromatic ketones. I received the catalyst *in situ*, and as a hydrogen source I initially used the azeotropic mixture of formic acid and triethylamine. The reduction was carried out in acetonitrile at 25 ^{o}C (method A in Scheme 7) and gave alcohols with low yield and low enantiomeric excess (Table 5). Taking into account the poor results of hydrogenation, I decided to perform this reaction using isopropanol as a hydrogen donor (method B).



Scheme 7. Asymmetric transfer hydrogenation of acetophenones using catalyst **49**.

Also in this version, the catalyst was prepared *in situ* by heating at 70 ^{o}C $[RuCl_2(benzene)]_2$ with amine **47** and KOH in 2-propanol at 70 ^{o}C. After 20 min. of stirring the solution of catalyst was cooled to room temperature and ketone was added to the reaction mixture. The reduction of the acetophenones was carried out at room temperature and the reaction progress was monitored by TLC as previously

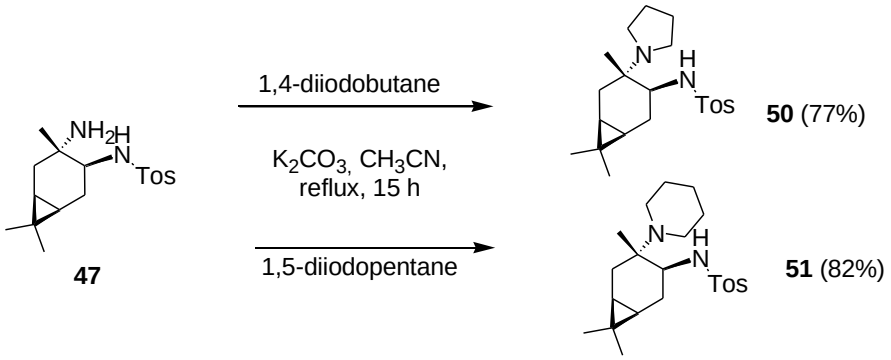
Table 5. The results of ATH reduction of ketones using catalyst **49**.

Cat.	X	Y	Time	Yield. (%)	ee (%)[c] ( )[d]
49[a]	H	H	6 days	22	32 (*S*)
49[a]	H	CH_3	6 days	5	36 (*S*)
49[a]	*o*-Cl	H	6 days	9	12 (*R*)
49[a]	*p*-Cl	H	6 days	16	23 (*S*)
49[a]	*o*-Br	H	6 days	25	9 (*R*)
49[a]	*p*-Br	H	6 days	27	16 (*S*)
49[a]	*p*-CH_3	H	6 days	32	36 (*S*)
49[a]	*p*-OCH_3	H	6 days	29	34 (*S*)
49[b]	H	H	24 h	62	64 (*S*)
49[b]	H	CH_3	24 h	77	56 (*S*)
49[b]	*o*-Cl	H	24 h	83	22 (*R*)
49[b]	*m*-Cl	H	24 h	75	48 (*S*)
49[b]	*p*-Cl	H	24 h	62	42 (*S*)
49[b]	*o*-Br	H	24 h	85	20 (*R*)
49[b]	*m*-Br	H	24 h	76	45 (*S*)
49[b]	*p*- Br	H	24 h	75	36 (*S*)
49[b]	*o*-CH_3	H	24 h	65	24 (*R*)
49[b]	*m*-CH_3	H	24 h	60	73 (*S*)
49[b]	*p*-CH_3	H	24 h	68	52 (*S*)
49[b]	*p*-OCH_3	H	24 h	74	71 (*S*)

[a] The reaction was carried out at room temperature using a ketone (2.40 mmol) in CH_3CN (1mL) and a formic acid-triethylamine mixture (5:2, 1 mL) with S/C = 100; [b] The reaction was carried out at room temperature using a ketone (2.40 mmol) in 2-propanol (1mL) and 0.1M KOH solution in 2-propanol (1 m L) with S/C = 100; [c] Determined by GC analysis using a Supelco cyclodextrin β-DEX 120 capillary column (20 m x 0.25 mm I.D. and 0.25 μm film thickness); [d] Determined by the sign of the specific rotation of the isolated product.

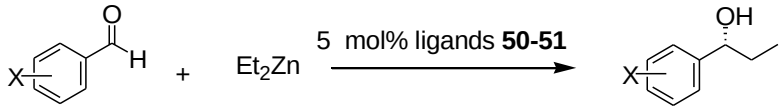
Under these conditions the reduction was much faster and gave alcohols with a high yield after 24 hours but the optical purity remained at a moderate level (Table 5).I obtained the best results of the asymmetric hydrogenation with catalyst **49** for unsubstituted and *m*-substituted acetophenones. I obtained the alcohols with a yield close to 80% and ee in the range of 30-73%. In the case of *ortho*-substituted ketones I observed a significant decrease in the enantioselectivity of the process, but with a retention of high chemical yield.

Wills showed that 1,2-diaminocyclohexane derivatives having a combination of a monothosylated amine and a tertiary amino group can be used as effective ligands in the addition of diethylzinc to benzaldehyde.[16] Therefore, I used amine **47** to synthesize this type of ligands (Scheme 8). I obtained ligands **50-51** with a high yield in the reaction between amine **47** and an appropriate diiodoalkane, in the presence of potassium carbonate.



Scheme 8. The synthesis of *N*-alkylated ligands **50-51**.

Then, I checked the catalytic activity of these compounds in the ethylation reaction with benzaldehyde derivatives (Scheme 9). The ligands containing tertiary amino groups gave products with a high chemical yield but with a moderate enantiomeric excess. A slightly better enantioselectivity was obtained using derivative **8**, which contained a piperidine ring (Table 6).



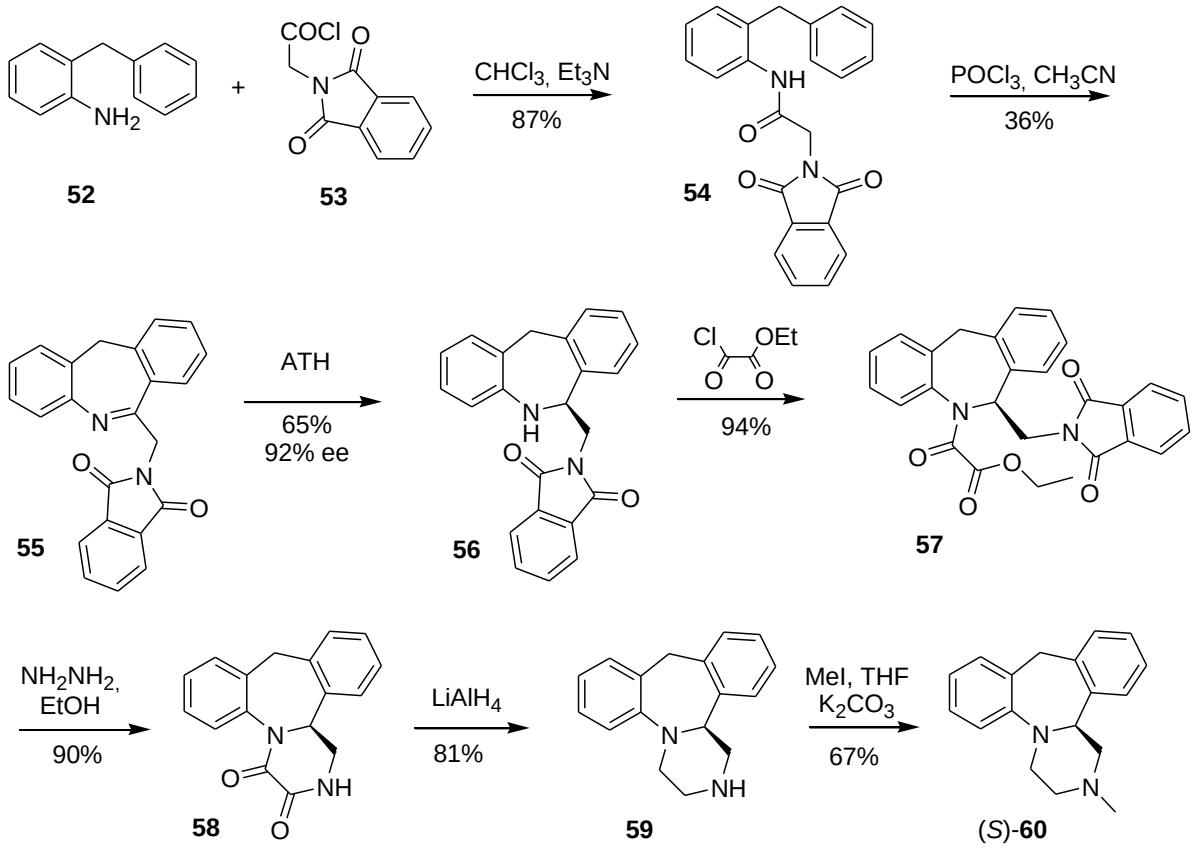
Scheme 9. The ethylation reaction of substituted benzaldehydes with ligands **50-51**.

Table 6. The results of the ethylation of substituted benzaldehydes with ligands **50-51**.

Ligand	X	Time (h)	Yield (%)	ee (%)[a] ()[b]
50	H	20	82	38 (*R*)
51	H	20	93	56 (*R*)
50	*p*-Cl	20	85	27 (*R*)
51	*p*-Cl	20	92	48 (*R*)
50	*p*-OCH_3	20	87	41 (*R*)
51	*p*-OCH_3	20	90	54 (*R*)

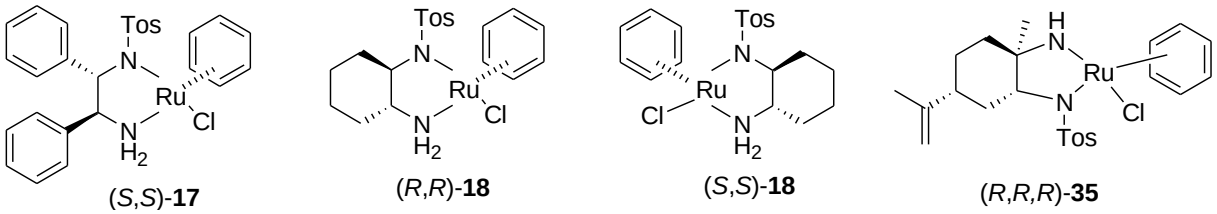
[a] Determined by GC analysis using a Supelco cyclodextrin β-DEX 120 capillary column; [b] Determined by the sign of the specific rotation of the isolated product.

As mentioned earlier, the collected experience during the asymmetric synthesis of aptazepine (publication **H1**) allowed me to obtain an enantiomerically pure mianserin. Mianserin is an active substance used in the treatment of depression and is used in pharmacotherapy as racemate, despite the dominant activity of the (*S*) isomer. Due to the lack of an enantioselective method of preparation, I decided to synthesize it based on the previously developed synthetic route of aptazepine (publication **H5**). The key step in a synthetic pathway is the introduction of a stereogenic center into the molecule, which I realized by the asymmetric hydrogenation of prochiral imine **55** (Scheme 10). I started the synthesis with cheap and easily available substrates: 2-beznylaniline **52** and *N*-phthalylglycyl chloride **53**. The condensation of the obtained amide **54** according to the Bischler-Napieralski method led to a prochiral imine **55** with a low yield of 36%. Therefore, the unreacted amide was recovered and used again to increase the overall yield of this reaction.



Scheme 10. The enantioselective synthesis of (*S*)-(+)-mianserin.

In the next step, I carried out the asymmetric reduction of the imine **55** under the ATH conditions, using chiral ruthenium complexes **17**, **18** and **35**, which I obtained by reacting benzeneruthenium chloride with an optically pure monotosylated 1,2-diamines (Figure 5). For the reduction, I initially used the catalyst **18** which contains (1*R*,2*R*)- or (1*S*,2*S*)-*N*-monotosyl-1,2-diaminocyclohexane as a chiral ligand. When the reaction was carried out in acetonitrile, I obtained the amine **56** with a low 11% yield and a moderate asymmetric induction 60% ee. The low yield probably resulted from the limited solubility of the imine in acetonitrile. Therefore, I decided to test solvents in which the substrate is better soluble.



(*S*,*S*)-**17** (*R*,*R*)-**18** (*S*,*S*)-**18** (*R*,*R*,*R*)-**35**

Figure 5. The structure of catalysts used in ATH reduction of imine **55**.

When the hydrogenation was made in dichloromethane, I obtained a product with a high 65% yield and a 92% ee (Table 7). The reduction in chloroform gave worse results (45% yield and 73% ee) than the reaction in dichloromethane, but the hydrogenation of imine **55** in DMF using (*R*,*R*)-**18** gave a product with the highest enantiomeric excess- 95%, but with only 26% of chemical yield. I obtained worse reduction results using complex **17** (72-73% ee), modified with *N*-tosyl-(1*S*,2*S*)-1,2-diphenylethylenediamine, regardless of the solvents used (Table 7). Finally, for the enantioselective reduction, I used to the ruthenium complex **35** modified with the amine which I developed earlier. I chose them from the group of complexes developed by me, because it showed the best enantioselectivity in the model reactions. This catalyst possesses a similar activity to catalyst **17** and gave the product with a 75% enantiomeric excess and a 52% yield.

Table 7. The results of asymmetric reduction of imine **55** under the ATH conditions.[a]

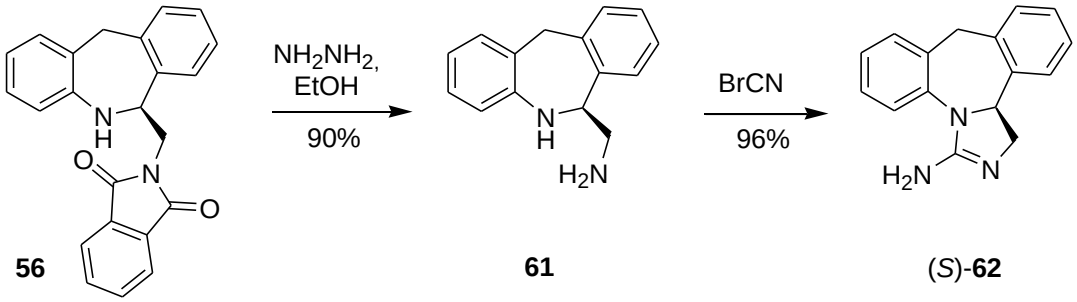
Cat.	Solvent	Time (h)	Yield (%)	$[\alpha]_D^{23}$	ee (%)[b], ()[c]
(*R*,*R*)-**18**	CH_3CN	72	11	+ 41.0	60 (*S*)
(*R*,*R*)-**18**	CH_2Cl_2	24	65	+62.8	92 (*S*)
(*S*,*S*)-**18**	CH_2Cl_2	24	63	-62.2	91 (*R*)
(*R*,*R*)-**18**	$CHCl_3$	24	45	+50.1	73 (*S*)
(*S*,*S*)-**18**	$CHCl_3$	24	47	- 49.3	72 (*R*)
(*R*,*R*)-**18**	DMF	24	26	+65.0	95 (*S*)
(*S*,*S*)-**17**	CH_3CN	74	0	-	-
(*S*,*S*)-**17**	CH_2Cl_2	24	51	-49.0	72 (*R*)
(*S*,*S*)-**17**	$CHCl_3$	24	56	- 50.3	73 (*R*)
(*S*,*S*)-**17**	DMF	24	23	- 50.1	73 (*R*)
(*R*,*R*,*R*)-**35**	CH_2Cl_2	24	52	+51.6	75 (*S*)
(*R*,*R*,*R*)-**35**	DMF	24	21	+ 42.1	62 (*S*)

[a] The reaction was carried out at 22-24 ^oC using imine **6** (0.284 mmol) in solvent (5 mL) and a formic acid-triethylamine mixture (5:2, 1 mL) with S/C = 50. [b] Determined by the value of the specific rotation of the isolated product. [c] Determined by the comparison with X-ray data.

Despite the high enantioselectivity of the reduction, I needed an enantiomerically pure amine **56** for the further synthetic steps. I obtained it by single crystallization of the enantioenriched sample above 75%. Next, the absolute configuration of amine **56** was determined based on the result of the X-ray analysis, which allowed to connect the sign of the optical rotation with the stereochemistry of the asymmetric carbon atom. In the subsequent steps of the mianserin synthesis, I used conditions previously developed for the aptazepine (Scheme 10). I converted

the enantiomerically pure amine **56** to the appropriate amide by reacting it with ethyl oxalyl chloride. Then, using hydrazine, I unblocked the amino function. The obtained intermediate cyclized spontaneously in the reaction medium to diketopiperazine **58**. I removed the carbonyl groups with lithium aluminum hydride and after the methylation of the amino function I obtained the enantiomer of (*S*)-(+)-mianserin **60**. I confirmed the optical purity of the final product by HPLC analysis using column with chiral stationary phase (Chiralcel OD-H).

Additionally, I used the optically pure amine **56** for the synthesis of epinastine, an active substance with antiallergic effect (Scheme 11). I removed the phthaloyl protecting group from compound **56** using hydrazine and then, in the reaction of diamine **61** with cyanogen bromide, I obtained the (*S*)-(+)-epinastine **62** with 96% yield.



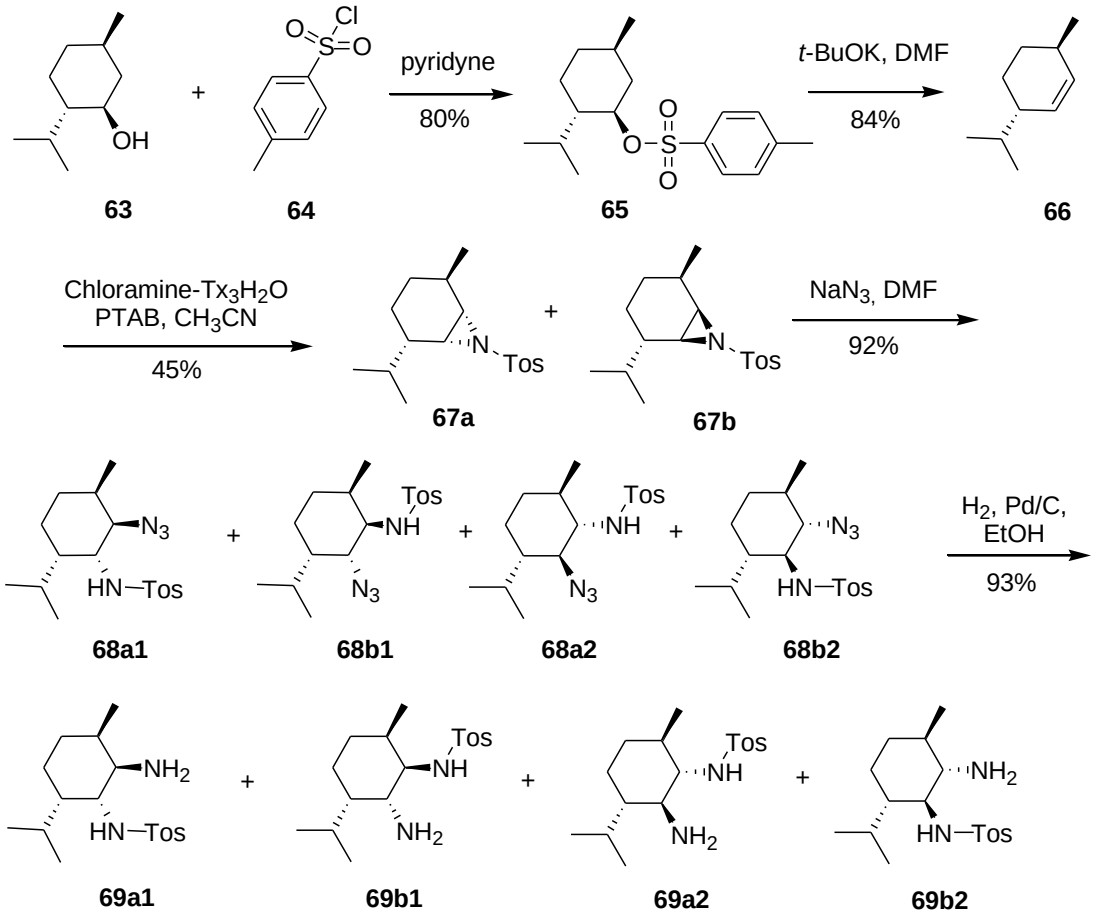
Scheme 11. The enantioselective synthesis of (*S*)-(+)-epinasine.

The developed synthetic pathway presented in publication **H5**, could be used for the enantioselective preparation of other mianserin and epinastine analogues variously substituted at the aryl rings. In the key synthetic step, I introduced the chirality to the molecule by asymmetric hydrogen transfer reaction to an endocyclic imine. Thanks to the use of the chiral ruthenium complexes, modified with optically pure monotosylated *trans*-1,2-diamines, the hydrogenation process takes place with a high enantioselectivity.

In the case of using the limonene for the synthesis of monothosylated derivatives of 1,2-diamines, I studied the effect of the methyl substituent, bonded with the same carbon atom as the free amine group, on asymmetric induction. In further studies, which I described in publications **H6** and **H7**, I analyzed the effect of the substituents located in the α-position in the relation to the amino groups (**H6**) and the replacement of the methyl substituent with the isopropyl group on the carbon attached to the free amino function (**H7**). To realize my project, I used natural menthol as a structural platform to synthesize the appropriate 1,2-diamines.

Firstly, I examined the effect of the remoteness of the alkyl substituents from carbon atoms associated with the amino groups (publication **H6**). Based on literature data, I converted the natural menthol into a *trans*-*p*-menth-2-ene **66**, which has a double bond in a suitable position for further functionalization (Scheme 12). I converted the unsaturated compound **66** to aziridines **67** using the previously described *N*-tosylaziridination reaction. In this reaction, the formation of equimolar *cis/trans*- aziridines mixture **67** with a 45% yield

was observed (based on ^{1}H NMR spectrum). In this case, the arrangement of the methyl and isopropyl substituents in the cyclohexane ring did not give any stereoselectivity in the aziridation process.



Scheme 12. The synthetic pathway of monotosylated diamines **69a,b**.

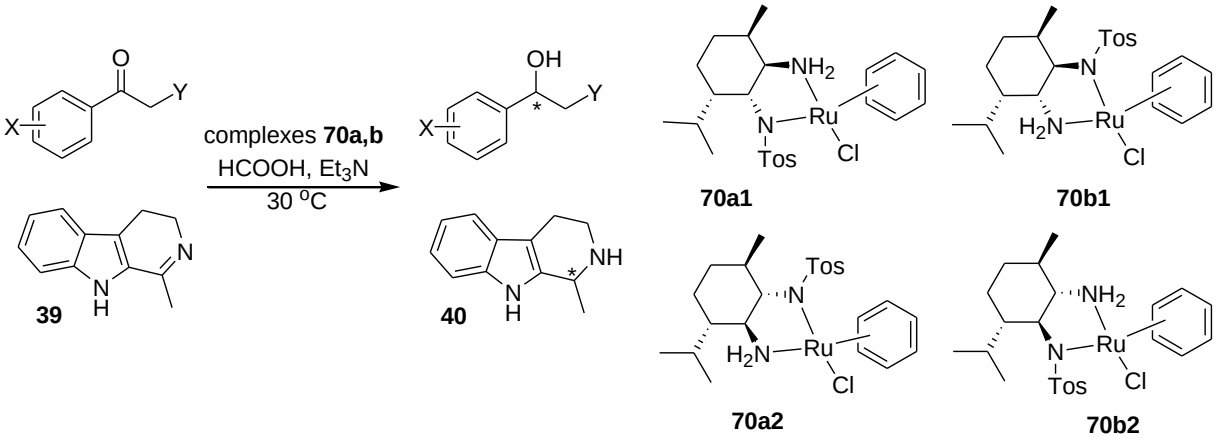
This aziridines are inactive in reaction with sodium azide when isopropanol/water mixture (1:1,v/v) was used as a solvent. The change of the solvent on DMF gave azides **68a,b** with a 92% yield. In this solvent the nucleophilic ring opening of *N*-tosylaziridines **67a**,**b** by the azide anion was almost regio- and diastereoselective at 24 ^{o}C. The HPLC analysis on a chiral stationary phase (Chiralcel OD-H) showed the presence of azido amine isomers **68a1** and **68b1** in 1:1 ratio and only traces of isomers **68a2** and **68b2**. Further studies showed that the stereoselectivity of this reaction strongly depends on temperature and the propagation of the azide isomer pair can be controlled using this parameter (Table 8). I separated the mixture of isomers **68a**,**b** by column chromatography into two pairs of azides: **68a1**, **68b1** and **68a2**, **68b2**. Next, I isolated the particular azides by several crystallizations of each pair from solvent mixtures and determined their absolute configuration by the single crystal X-ray analysis. Finally, I hydrogenated the pure regioisomers **68a,b** over Pd/C and obtained the desired monotosylated diamines **69a,b** with a yield up to 93%.

Table 8. The distribution of azides **68** depends on reaction temperature.

Temp. (^{o}C)	Yield (%)[a]			
	68a1	**68b1**	**68a2**	**68b2**
24	48	47	4	1
45	48	47	5	1
65	45	46	8	1
85	39	43	13	4
105	16	28	32	24
125	13	20	41	26
145	16	21	27	23

[a] Determined by HPLC analyses using Chiracel OD-H column.

In order to evaluate the potency of amines **69a,b** as chiral inductors I used them in the Ru-catalyzed asymmetric hydrogen transfer reaction to some aryl ketones and endocyclic imine as a model transformation. The ruthenium complexes were prepared *in situ* by mixing $[RuCl_2(benzene)]_2$ with monotosylated diamines **69a,b** and triethylamine in acetonitrile (Scheme 13).



Scheme 13. The ATH reduction of aromatic ketones and imine using complexes **70a,b**.

As shown in Tables 9 and 10, the ruthenium catalysts **8a,b** are much more efficient in the reduction of ß-carboline than in ketones. The enantioselective hydrogenation of aryl ketones gave appropriate alcohols with moderate yield (up to 67%) and enantiomeric enrichment (up to 60%). The best results were obtained for complex **70b2** in which the NH-Tos group has an equatorial orientation and is bonded to the carbon atom adjacent to the isopropyl group. The complex **70a1**, having the NH-Tos group connected with the same carbon atom but in an axial position, gave products with a slightly lower yield and a comparable enantioselectivity. In the case of the imine reduction, the substrate was consumed completely after 14 hours. As observed previously, complex **70b2** was the best and gave amine **40** with a 68% ee. Importantly, all four catalysts have similar activity and give products with the same configuration. The results of the reduction indicate that both the orientation and the relative position of the NH_2 and NH-Tos groups in complexes **70a,b** have no effect on the configuration of the final product. Apparently, the crucial role plays the stereochemistry of

methyl and isopropyl substituents at the cyclohexane moiety, which are in a *trans* position towards each other.

Table 9. The results of the ATH reduction of ketones with catalysts **70a,b**.[a]

Cat.	X	Y	Time (h)	Yield (%)	ee (%)[b,c]
70a1	H	H	96	48	60 (*S*)
70b1	H	H	96	36	52 (*S*)
70a2	H	H	96	38	52 (*S*)
70b2	H	H	96	53	60 (*S*)
70a1	H	CH_3	96	37	44 (*S*)
70b1	H	CH_3	96	26	40 (*S*)
70a2	H	CH_3	96	29	50 (*S*)
70b2	H	CH_3	96	40	56(*S*)
70a1	*o*-CH_3	H	96	27	24 (*S*)
70b2	*o*-CH_3	H	96	29	27 (*S*)
70a1	*m*-CH_3	H	96	32	44 (*S*)
70b2	*m*-CH_3	H	96	35	50 (*S*)
70a1	*p*-CH_3	H	96	37	47 (*S*)
70b2	*p*-CH_3	H	96	43	58 (*S*)
70a1	*m*-Br	H	96	62	42 (*S*)
70b2	*m*-Br	H	96	67	51 (*S*)

[a] The reaction was carried out at 30 ^oC using a ketone (1.10 mmol) in CH_3CN (1mL) and a formic acid-triethylamine mixture (5:2, 1 mL) with S/C = 100; [b] Determined by HPLC analysis using a Chiralcel OD-H column; [c] Determined by the sign of the specific rotation of the isolated product.

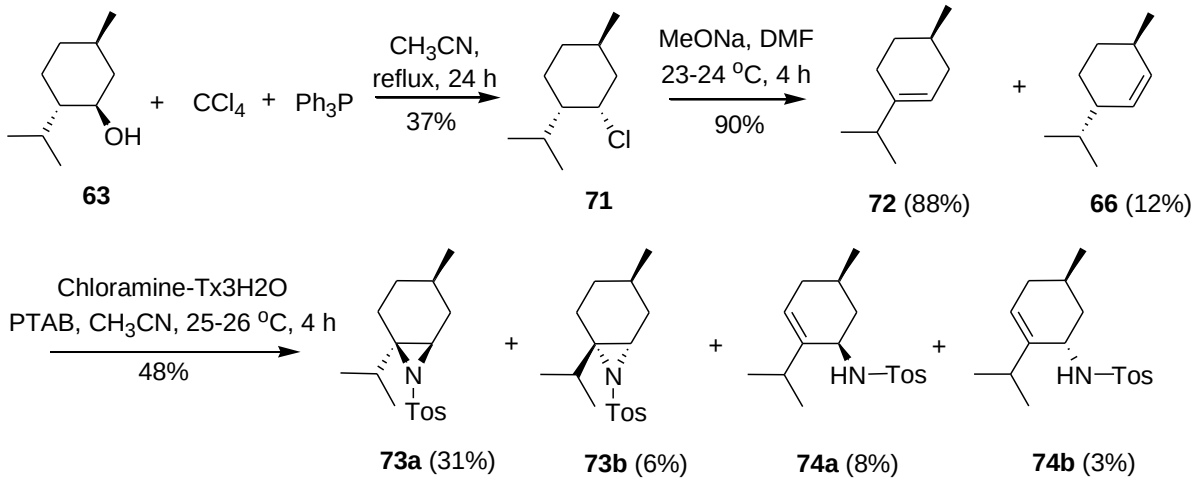
Table 10. The results of the ATH reduction of 1-methyl-3,4-dihydro-ß-carboline with catalysts **70a,b**.[a]

Cat.	Time (h)	Yield (%)	ee (%)[b,c]
70a1	14	100	60 (*R*)
70b1	14	100	42 (*R*)
70a2	14	100	59 (*R*)
70a2	14	100	58 (*R*)[d]
70a2	14	100	54 (*R*)[e]
70b2	14	100	68 (*R*)

[a] The reaction was carried out at 30 ^oC using imine (0.30 mmol) in CH_3CN (1mL) and a formic acid-triethylamine mixture (5:2, 0.6 mL) with S/C = 50; [b] Determined by HPLC analysis using the Chiralcel OD-H column; [c] Determined by the sign of the specific rotation of the isolated product; [d] The reaction was carried out in 2-propanol; [e] The reaction was carried out in CH_2Cl_2.

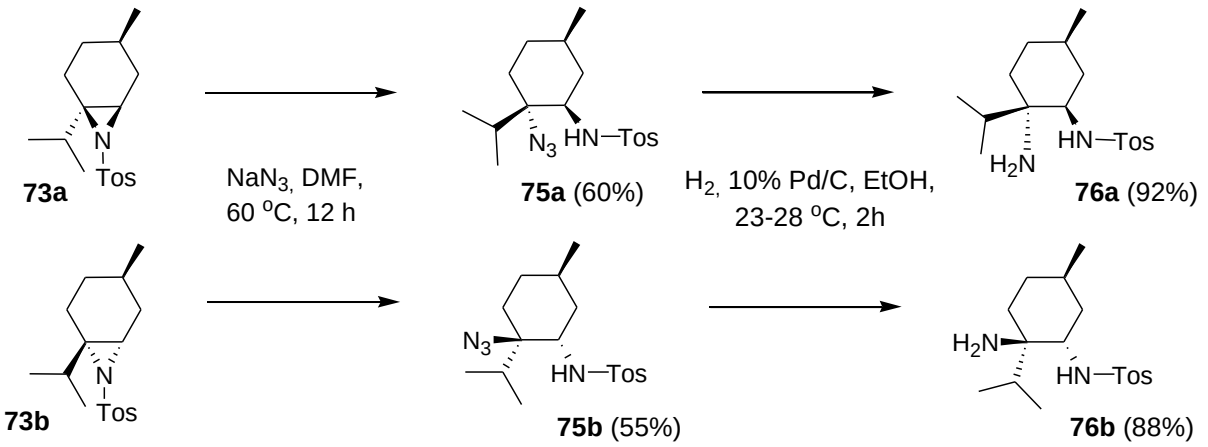
In the last publication **H7**, I checked the effect of the replacement of the methyl substituent bonded to a carbon atom with the amino function, with an isopropyl group. Also in this case, I used the stereochemistry of natural menthol to get a monotosylated 1,2-diamine

system after a few modifications, as shown in Schemes 14-15. For the selective introduction of a double bond at the carbon atom bonded to the isopropyl substituent, I converted natural menthol into neomenthyl chloride **71** (Scheme 14). After optimizing the dehydrochlorination reaction conditions of neomenthyl chloride I found that sodium methoxide gave the best results and led to *p*-menth-3-ene **72** with a purity of 88%, which was contaminated with isomeric *p*-menth-2-ene **66**. This mixture of menthenes could not be separated and therefore I used it without further purification for the aziridination reactions under the previously tested conditions.



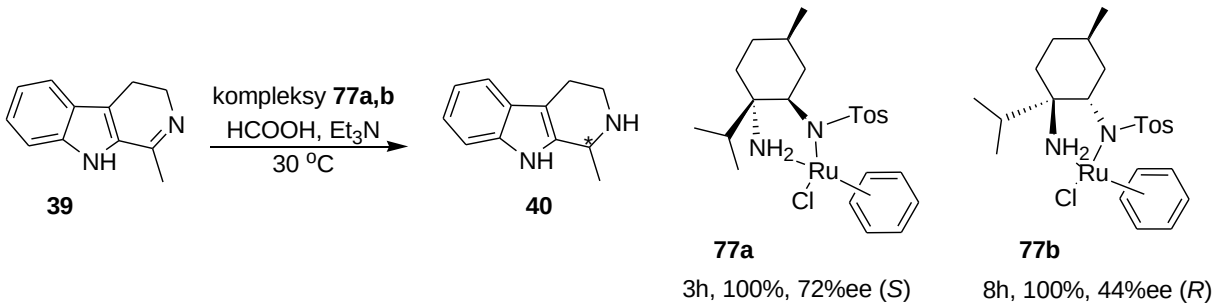
Scheme 14. The synthesis of aziridines **73a,b**.

The reaction between *p*-menth-3-ene **72** and Chloramine-T trihydrate in the presence of phenyltrimethylammonium tribromide carried out at 25-26 ^{o}C resulted in the formation of a mixture of *cis/trans*- aziridines **73a,b**, which were isolated with a 37% yield. Additionally, the dehydrobromination products **74a,b** were isolated with a 11% yield. Based on the ^{1}H NMR analysis, I found that the ratio of aziridines **73** to unsaturated derivatives **74** is 70:30 and the ratios of **73a:73b** and **74a:74b** are ca 78:22. When the reaction was carried out at 45 ^{o}C the main product **73** was isolated in 25% yield with a similar ratio of aziridines. I separated the mixture of compounds **73** and **74** by column chromatography on silica-gel and then obtained the individual isomers **73,b** and **74a,b** by a fractional crystallization. The absolute configuration of compounds **73a** and **74a** was determined by single crystal X-ray analysis. Then, in the reaction of aziridines **73a** and **73b** with sodium azide in dimethylformamide, I obtained single isomers of azides **75a** and **75b**, which indicates the regio- and diastereoselectivity of this reaction in both cases (Scheme 15). At the last step, I hydrogenated the pure isomers of **73a** and **73b** over 10% Pd/C and obtained the diamines **76a** and **76b** with high yields. I obtained suitable crystals for X-ray analysis for azide **75a** and amine **76b** and their absolute configuration was determined by the single crystal X-ray analysis.



Scheme 15. The conversion of aziridines **73a,b** into 1,2-diamines **76a,b**.

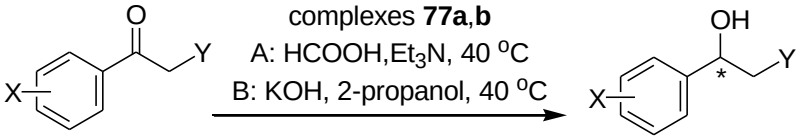
In order to evaluate the utility of the obtained amines **76a** and **76b** as chiral inductors, I prepared the Ru(II) complexes **77a** and **77b** and tested them against 1-methyl-3,4-dihydro-ß-carboline and various model aromatic ketones under the asymmetric transfer hydrogenation conditions. As previously, these ruthenium complexes were prepared *in situ* by mixing $[RuCl_2(benzene)]_2$ with monotosylated diamines **76a** and **76b** and triethylamine in acetonitrile or by heating the metal precursor with the ligand in 2-propanol at 80 °C. Initially, I tested the model reduction of 1-methyl-3,4-dihydro-ß-carboline using a HCOOH/Et_3N mixture as the hydrogen source (Scheme 16). The catalyst **77a** in which the methyl and isopropyl substituents are in the *cis*-position showed a significantly higher asymmetric induction and gave the amine with a 72% ee.



Scheme 16. The reduction of 1-methyl-3,4-dihydro-ß-carboline with complexes **77a,b**.

Taking into consideration a promising activity of the tested complexes **77a,b** in imine reduction, I applied them to a model hydrogenation of several aryl ketones. Initially, I carried out the reaction under the same conditions as for the imine reduction (method A, Scheme 17). Unfortunately, I observed a low activity of catalysts **77a,b** in the reduction using formic acid. After 96 hours I obtained the appropriate alcohols with a 2-15% yield and with an enantiomeric excess of 7-32% (Table 11). Therefore, I examined the catalytic activity of compounds**77a,b** under the basic conditions using 2-propanol as a hydrogen donor (method B, Scheme 17). The replacement of formic acid with 2-propanol gave much better results. In most cases the alcohols were obtained with a moderate enantiomeric purity and with a good yield. The best results in the ketones reduction were obtained for complex **77b**. The enantiomeric enrichment increased to 83-84% and the yield increased to 32-46%.

Interestingly, the hydrogenation of ketones using complex **77a** in 2-propanol gave the alcohols with reversed configurations.



Scheme 17. The ATH of some aromatic ketones using complexes **77a,b**.

Table 11. The ATH reduction of ketones with catalysts **77a,b**.

Cat.	X	Y	Time (h)	Yield (%)	ee (%)[c,d]
77a[a]	H	H	96	13	32 (*S*)
77a[b]	H	H	48	32	46 (*R*)
77b[a]	H	H	96	13	17 (*S*)
77b[b]	H	H	48	46	83 (*S*)
77a[a]	H	CH_3	96	5	26 (*S*)
77a[b]	H	CH_3	48	14	23 (*R*)
77b[a]	H	CH_3	96	5	24 (*S*)
77b[b]	H	CH_3	48	17	84 (*S*)
77a[a]	*o*-CH_3	H	96	2	12 (*R*)
77a[b]	*o*-CH_3	H	48	10	50 (*R*)
77b[a]	*o*-CH_3	H	96	3	10 (*S*)
77b[b]	*o*-CH_3	H	48	14	63 (*S*)
77a[a]	*m*-CH_3	H	96	7	7 (*S*)
77a[b]	*m*-CH_3	H	48	28	72 (*R*)
77b[a]	*m*-CH_3	H	96	11	9 (*S*)
77b[b]	*m*-CH_3	H	48	32	81 (*S*)
77a[a]	*p*-CH_3	H	96	5	24 (*S*)
77a[b]	*p*-CH_3	H	48	10	26 (*R*)
77b[a]	*p*-CH_3	H	96	7	21 (*S*)
77b[b]	*p*-CH_3	H	48	12	76 (*S*)
77a[a]	*m*-Br	H	96	28	6 (*S*)
77a[b]	*m*-Br	H	48	62	56 (*R*)
77b[a]	*m*-Br	H	96	31	12 (*S*)
77b[b]	*m*-Br	H	48	75	67 (*S*)

[a] The reaction was carried out at 40 °C using a ketone (0.55 mmol) in CH_3CN (1mL) and a HCOOH-Et_3N mixture (5:2, 0.5 mL) with S/C = 50; [b] The reaction was carried out at 40 °C using a ketone (0.55 mmol) in 2-propanol (1mL) and a 0.1M KOH in 2-propanol solution (0.5 mL) with S/C = 50; [c] Determined by HPLC analysis using a Chiralcel OD-H column; [d] Determined by the sign of the specific rotation of the isolated product.

The difference in the activity of the complexes **77a,b** in the reduction of imine and ketone using formic acid as a hydrogen source can be rationalized based on a mechanistic consideration. In the case of the imine reduction, the ionic mechanism proposed by Wills[27,28] shows that a six-membered transition state is not operating and therefore even strongly sterically hindered catalysts like **77a,b** can effectively transfer a hydrogen to a protonated imine. During the reduction of ketones the formation of a six-membered transition state may be more difficult and therefore the active hydride responsible for the hydrogen transfer could become partially decomposed in the reaction environment. In the case of complexes **77a,b**, the reduction of ketones carried out with formic acid as a hydrogen source gave in both cases alcohols of (*S*) configuration. This suggests that also here the direction of the asymmetric induction depends mainly on the stereochemistry of the alkyl substituents in the cyclohexane ring. The activation of ruthenium complexes **77a,b** and the observed change in the configuration of the obtained products in the case of derivative **77a** during the reduction with 2-propanol probably results from the conformational change of the cyclohexane unit. Apparently, under these conditions, the less sterically hindered conformers were formed. These conformers were able to create a six-membered transition state and the orientation of the isopropyl substituent determined the direction of the asymmetrical induction.

Summary

In this dissertation, I presented the results of the research included in a series of seven thematically related publications, which are my contribution to the development of stereoselective organic synthesis.

The most important achievements of my dissertation include:

- The development of a multi-step synthesis of monosylated 1,2-diaminocyclohexane derivatives, analogues of *trans*-1,2-diaminecyclohexaness, based on the structural frame of natural monoterpenes: (+)-limonene, (+)-3-karen and menthol.
- The realization and optimization of individual synthetic steps of the family of six monotosylated *trans*-1,2-diamines based on the (+)-limonene structure.
- The demonstration of a high catalytic activity of 1,2-diamines, limonene derivatives, as chiral inducers in the asymmetric hydrogen transfer reaction to selected aromatic ketones and cyclic imines. Some of the ruthenium complexes, obtained on the basis of monotosylated diamines, led to the products of enantioselective reduction with quantitative yields and an enantiomeric excess above 90%.
- The realization and optimization of individual synthetic steps of monotosylated *trans*-1,2-diamine based on the (+)-3-carene structure.
- The demonstration of a moderately high catalytic activity of this 1,2-diamine, as a chiral inductor in the asymmetric hydrogen transfer reaction to selected aromatic ketones. Demonstration of a significant improvement in the activity of the ruthenium complex, chelated with carene based diamine, after the change of the hydrogen source from formic acid to 2-propanol.

- The synthesis of alkyl derivatives of the above 1,2-amines mentioned above and demonstration of their activity in the enantioselective addition of diethylzinc to benzaldehyde.

- The realization and optimization of individual synthetic steps of four monotosylated *trans*-1,2-diamines, which have the substituents located in the α-position in the relation to the amino groups, based on the menthol structure.

- The demonstration of moderately high activity of the above four amines as chiral inducers in the asymmetric hydrogen transfer reaction to selected aromatic ketones and cyclic imines. The ruthenium complexes chelated with monotosylated 1,2-diamines derived from menthol led to the alcohols with quantitative yields up to 67% and an enantiomeric excess up to 60%. The demonstration of the key role of the alkyl substituents in the cyclohexane ring for the direction of asymmetric induction during enantioselective reduction of imines and ketones.

- The realization and optimization of individual synthetic steps of two monotosylated *trans*-1,2-diamines, possessing the isopropyl substituent bonded with carbon atom with amino group, based on menthol structure.

- The demonstration of moderately good activity of the two amines mentioned above as chiral ligands for the construction of ruthenium complexes used in the reaction of asymmetric hydrogen transfer to selected imines and aromatic ketones. The demonstration of a significant improvement in the activity of the ruthenium catalyst after the change of the hydrogen donor from formic acid to 2-propanol. The demonstration of the key role of the alkyl substituents for the direction of asymmetric induction during the enantioselective reduction of imines and ketones.

- The demonstration of the potential of natural monoterpenes, by the example of (+)-limonene, (+)-3-carene and menthol, for the synthesis of optically pure monotosylated *trans*-1,2-diamines derivatives.

- The development and realization of the enantioselective synthesis of active substances with antidepressant (aptazepine and mianserin) and antiallergic (epinastine) effect based on the asymmetric hydrogen transfer process, catalyzed by chiral ruthenium complexes. The ruthenium complexes used in the reduction of imines, modified with monotosylated *trans*-1,2-diamines prepared by me, were characterized by a high degree of asymmetric induction, comparable in the selected cases to the most active ruthenium catalysts.

- The demonstration that the developed synthetic pathway can be used for the enantioselective preparation of other mianserin and epinastine analogues variously substituted in the aryl rings.

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5. Other scientific publications and achievements

a) Bibliographic summary of scientific achievements

Total number of publications: **33**

Total number of publications after Ph.D. degree: **26**

Total impact factor (according to the year of publication): **77.701**

Citation report based on Web of Science at 22nd of September 2018:

Total number of citations: **191**

Total number of citations (without self-citations): **157**

Hirsch index: **6**

Within the research projects to date, I explored the various topics in the field of organic synthesis. During my master's thesis, I made a synthesis and examined the phase polymorphism of rod-like liquid crystals, thiobenzoate derivatives (**M1**) under the supervision of Ph.D. Mirosława Ossowska-Chruściel. My doctoral thesis was focused on the enantioselective synthesis of tetrahydro-β-carboline and tetrahydroisoquinoline derivatives (**M2-M6**, **C1**) (Prof. Zbigniew Czarnocki). Later in my career, I focused mainly on three research areas related to the scientific projects realized in our team. The first research topic concerned the synthesis and use of chiral 1,2-diamine ligands in asymmetric synthesis, as described in the presented dissertation (**H1-H7**). The second direction of research, which I devoted a lot of attention, was the study of the phenomenon of atropisomerism in derivatives of oligoarylpyridine (**P2**, **P5-P8**, **P10**, **P17-18**, **C2**). The realization of the third research branch, consisted of the stereoselective synthesis of cyclolignans, podophyllotoxin analogs (**P4, P13, P15**). In 2016 I took a short-term postdoctoral internship, during which I was involved in the synthesis of photoinitiators for polymerization reactions (**P11, P14**). Recently, I started the collaboration with Ph.D. Daniel Szulczyk in the field of research on heterocyclic compounds with antimicrobial activity (**P16**). Additionally, I participated in several smaller projects, which were the basis for several publications (**P1, P3, P9, P12**).

b) List of publications before Ph.D. degree (expect these listed in chapter 4) published in journals from the Journal Citation Reports database; IF according to the year of publication

M1. M.D. Ossowska-Chruściel*, **P. Roszkowski**, A. Rudzki, J. Chruściel,

„The influence of terminal chlorine on the mesomorphic properties of new thiobenzoates containing two and three benzene ring”,

Liquid Crystals **2005**, 32, 877-887, IF = 1.432.

M2. I. Matuszewska, A. Leniewski, **P. Roszkowski**, Z. Czarnocki*,

„Synthesis of novel class of fatty acids-derived isoquinolines”,

Chemistry and Physics of Lipids **2005**, 135, 131-145, IF = 2.351.

M3. P. Roszkowski, K. Wojtasiewicz, A. Leniewski , J. K. Maurin, T. Lis, Z. Czarnocki*,

„Enantioselective synthesis of 1-substituted tetrahydro-β-carboline derivatives *via* the asymmetric transfer hydrogenation”,

Journal of Molecular Catalysis A: Chemical **2005**, 232, 143-149, IF = 2.348.

M4. P. Roszkowski, J. K. Maurin, Z. Czarnocki*,

„Enantioselective synthesis of (*R*)-(-)-praziquantel (PZQ)”,

Tetrahedron: Asymmetry **2006**, 17, 1415-1419, IF = 2.468.

M5. P. Roszkowski, J. Szawkało, A. Zawadzka, Z. Czarnocki*,

„Enantioselective synthesis of β-carboline and isoquinoline derivatives *via* the asymmetric transfer hydrogenation”,

J. Mex. Chem. Soc. **2006**, 50, Special Issue 1, 122, IF = brak, IF (2017) = 0.643.

M6. P. Roszkowski, Z. Czarnocki*,

„Selected recent developments in the enantioselective reduction of imines by asymmetric transfer hydrogenation”,

Mini Review in Organic Chemistry **2007**, 4, 190-200, IF = 2.000.

c) List of publications after Ph.D. degree (expect these listed in chapter 4) published in journals from the Journal Citation Reports database; IF according to the year of publication

P1. K. Piwowarczyk, A. Zawadzka, **P. Roszkowski**, J. Szawkało, A. Leniewski, J.K. Maurin, D. Kranz, Z. Czarnocki*,

„Enantiomers of (2*R**,3*R**)-1-methyl-5-oxo-2-phenyltetrahydro-1-*H*-pyrrolidine-3-carboxylic acid as novel chiral resolving agents”,

Tetrahedron: Asymmetry **2008**, 19, 309-317, IF = 2.796.

P2. P. Roszkowski, D. Błachut, J. K. Maurin, M. Woźnica, J. Frelek, F. Pluciński, Z. Czarnocki*,

„Atropisomerism in 3,4,5-tri-(2-methoxyphenyl)-2,6-lutidine”,

Eur. J. Org. Chem. **2013**, 7867-7871, IF = 3.154.

P3. D. Zając, G. Spolnik, **P. Roszkowski**, W. Danikiewicz, Z. Czarnocki, M. Pokorski,

„Metabolism of *N*-Acylated-Dopamine”,

PLoS ONE **2014**, 9(1), e85259, IF = 3.234.

P4. K. Lisiecki, K. K. Krawczyk, **P. Roszkowski**, J. K. Maurin, Z. Czarnocki*,

„Formal synthesis of (−)-podophyllotoxin through the photocyclization of an axially chiral 3,4-bisbenzylidene succinate amide ester– a flow photochemistry approach”,

Org. Biomol. Chem. **2016**, 14, 2, 460-469, IF = 3.564.

P5. M. Górecki, **P. Roszkowski***, D. Błachut, J. K. Maurin, A. Budzianowski, J. Frelek, Z. Czarnocki,

„Atropisomerism in Mono- and Diaryl-substituted 4-amino-2,6-lutidine”,

Eur. J. Org. Chem. **2016**, 2966-2971, IF = 2.834.

P6. J. Szawkało, D. Błachut*, **P. Roszkowski**, P. Pomarański, J. K. Maurin, A. Budzianowski, Z. Czarnocki,

„New stable atropisomers derived from 2,4,6-collidine and related compounds",

Tetrahedron **2016**, 72, 6779-6787, IF = 2.651.

P7. P. Pomarański, S. Samanta, **P. Roszkowski**, J. K. Maurin, Z. Czarnocki*,

„ Enantioselective synthesis of axially chiral 3-bromo-4-alkoxy-2,6-dimethyl-5-(naphthalen-1-yl)-pyridines *via* an asymmetric Suzuki-Miyaura cross-coupling reaction",

Tetrahedron Lett. **2016,** 57, 4713-4717, IF = 2.193.

P8. D. Błachut*, J. Szawkało, P. Pomarański, **P. Roszkowski**, J.K. Maurin, Z.Czarnocki,

„Efficient Synthesis of Differently Substituted Triarylpyridines with the Suzuki-Miyaura Cross-coupling Reaction",

Arkivoc **2017,** part ii, 369-389, IF = 1.048.

P9. M. Dobrowolski*, **P. Roszkowski**, M. Struga, D. Szulczyk,

„The unexpected product of Diels-Alder reaction between"indanocyclon" and maleimide",

J. Mol. Structure **2017**, 1130, 573-578, IF = 2.011.

P10. P. Pomarański, **P. Roszkowski**, J.K. Maurin, A. Budzianowski, Z. Czarnocki*,

„Convenient synthesis of selected meta- and ortho- substituted pentaarylpyridines via the Suzuki-Miyaura cross-coupling reaction",

Tetrahedron Lett. **2017**, 58, 462-465, IF = 2.125.

P11. P. Roszkowski, M. Sahin, S. Ayalur-Karunakaran, C. Gammer, S. Schlogl, W. Kern, K. Krawczyk*,

„ Synthesis and evaluation of new radical photoinitiators bearing trialkoxysilyl groups for surface immobilization",

Polymer **2017**, 129, 207-220, IF = 3.483.

P12. S. Ahmad, L. Shukla, J. Szawkało, P. Roszkowski, J. K. Maurin, Z. Czarnocki*,

„Synthesis of novel chiral guanidine catalyst and its application in the asymmetric Pictet-Spengler re action",

Cat. Commun. **2017**, 89, 44-47, IF = 3.463.

P13. K. Lisiecki, K. K. Krawczyk, **P. Roszkowski***, J. K. Maurin, A. Budzianowski, Z. Czarnocki,

„ Unusual visible-light photolytic cleavage of tertiary amides during the synthesis of cyclolignans related to podophyllotoxin",

Tetrahedron **2017**, 73, 6316-6328, IF = 2.377.

P14. M. Sahin, K, K. Krawczyk, **P. Roszkowski**, J. Wang, B. Kaynak, W. Kern, S. Schlögl*, H. Grützmacher,

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a) List of publications after Ph.D. degree (expect these listed in chapter 4) published in journals outside the Journal Citation Reports database

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