# BULGARIAN ACADEMY OF SCIENCES

INSTITUTE OF ORGANIC CHEMISTRY WITH CENTRE FOR PHYTOCHEMISTRY

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# CHIRAL AMINOBENZYL-NAPHTHOLS AND -QUINOLINOLS AND DIHYDRO-1,3-NAPHTHOXAZINES - SYNTHESIS AND CATALYTIC APPLICATIONS

**DISSERTATION ABSTRACT**

submitted in fulfilment of

the requirements for the degree of

**PHILOSOPHIAE DOCTOR**

**(PhD)**

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Sofia, 2023

The synthetic research presented in this thesis was performed in the “Organic chemistry and Stereochemistry” Laboratory, Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences (IOCCP-BAS).

The NMR experiments were conducted in the NMR Centre at IOCCP-BAS.

The X-ray crystallographic analysis were conducted in the Institute of Mineralogy and Crystallography “Acad. Ivan Kostov”, Bulgarian Academy of Sciences.

The studies on biological activity were conducted in the Faculty of Biology of the SU "St. Kliment Ohridski".

The thesis was discussed and directed for defense by colloquium "Natural and synthetic biologically active compounds" at IOCCP-BAS on December 14th 2023.

The thesis consists of **220** pages, including **11** tables, **34** figures, and **112** schemes. The bibliography is based on **187** references. The results have been published in **3** scientific publications and presented at **7** scientific forums.

The numbering of sections, figures, tables, schemes, and compounds in the abstract are in conformity with those presented in the thesis.

The thesis defense will be held at a public session on ……. at …….. h in IOCCP-BAS, hall 111, Acad. G. Bonchev str., block 9, Sofia, Bulgaria.

The dissertation materials are available to those interested in IOCCP-BAS, room 206, Acad. G. Bonchev str., block 9, Sofia, Bulgaria.

# 1. INTRODUCTION

Multicomponent reactions are a modern tool for fast, easy and efficient preparation of structurally diverse multifunctional compounds in one step. This makes them an attractive area for application-oriented development. The pharmaceutical industry applies multicomponent reactions to generate libraries of multifunctional molecules and evaluate their activity in the process of developing new drugs. The search for new drug candidates aimed, for example, at the treatment of pathogens developing resistance, is directly dependent on the ability of medicinal chemistry to generate series of new compounds with diverse structural characteristics. Economic, regulatory and societal factors are increasingly driving the pharmaceutical industry towards more sustainable production methods, which is achieved by applying the principles of green chemistry. In this process, multicomponent reactions have a high potential for realizing environmentally friendly production processes of pharmaceutical products. From the point of view of medicinal chemistry, it is very important, in the process of synthesis of new compounds from prochiral substrates, to be able to generate enantiomerically (diastereoisomerically) pure products, due to the known influence of stereochemistry on the biological activity of substances. A significant part of the efforts of modern experimental organic chemistry is related to the implementation of enantioselective variants of almost every known chemical reaction. Multicomponent reactions are an essential unit in the development of new biologically active compounds, including structures possessing chirality, which explains the growing interest in them in recent years.

The *Mannich* reaction is one of the commonly applied multicomponent reactions and is a classic method of C–C bond formation in organic chemistry. The *Mannich* reaction is applicable to the preparation of dihydro-1,3-naphthoxazines by condensation of the naphthol component, amine and formaldehyde. This class of compounds exhibits a wide spectrum of biological activity. The compounds are used as intermediates for the synthesis of *N*-substituted aminonaphthols and nitrogen-bridged heterocyclic systems. Of great importance are the enantioselective variants of the reaction. There are only a few examples of the preparation of 1,3-O,N-heterocycles using chiral amines.

Certain variations have been developed in the classical *Mannich* reaction. When replacing formaldehyde with an aromatic aldehyde, and compounds with a mobile hydrogen atom – with electron-rich aromatic compounds, such as phenol, 1- or 2-naphthol, quinolinol or isoquinolinol, a three-component *Betti* condensation takes place. An important feature of the *Betti* reaction is that it proceeds with high diastereoselectivity when the amine used is chiral. Carrying out *Betti* condensation with enantiomerically pure amines is a fruitful research topic. In this approach, the presence of a

known stereogenic center at the amine induces the formation of a new stereogenic center with high stereoselectivity. The formation of aminobenzylnaphthols with two stereogenic centers is achieved.

The main set of chiral aminonaphthols, aminobenzylnaphthols and their analogues are used in asymmetric syntheses as ligands or auxiliary compounds, as well as intermediates for obtaining biologically active substances. Of particular interest are the applications in which such compounds are used as ligands for enantioselective nucleophilic addition reactions of nucleophilic reagents to carbonyl compounds, whereby chiral secondary alcohols are obtained. Chiral secondary alcohols are valuable intermediates in asymmetric organic synthesis for obtaining other chiral products – halogen-, thio- and phosphine derivatives, amines, ethers, esters, heterocycles, etc.

In asymmetric synthesis and catalysis, considerable resources are devoted to the development of strategies for the synthesis of new chiral ligands (modifiers) that are suitable for diverse applications. To date, no universal ligands or reagents applicable to the various types of enantioselective transformations have been synthesized. The efficiency of a given chiral modifier or catalyst (ligand) is usually high only for a specific reaction.

*Mannich* and *Betti* condensations provide significant opportunities for the synthesis of chiral compounds. Through their application, structurally diverse chiral multifunctional compounds were synthesized, which were used in the so-called asymmetric catalysis and have been successfully applied to achieve high asymmetric induction in addition reactions of organozinc reagents to aldehydes. In the present thesis, efforts are directed to use these condensation reactions for the synthesis of new chiral compounds that can be applied as ligands in the enantioselective addition of diethylzinc to aldehydes.

# 2. GOALS AND OBJECTIVES

In this dissertation, the synthesis of new chiral, non-racemic dihydro-1,3-naphthoxazines and aminobenzyl-naphthols and -quinolinols is planned, as well as their applicability as ligands in enantioselective reactions.

The following specific experimental tasks were set:

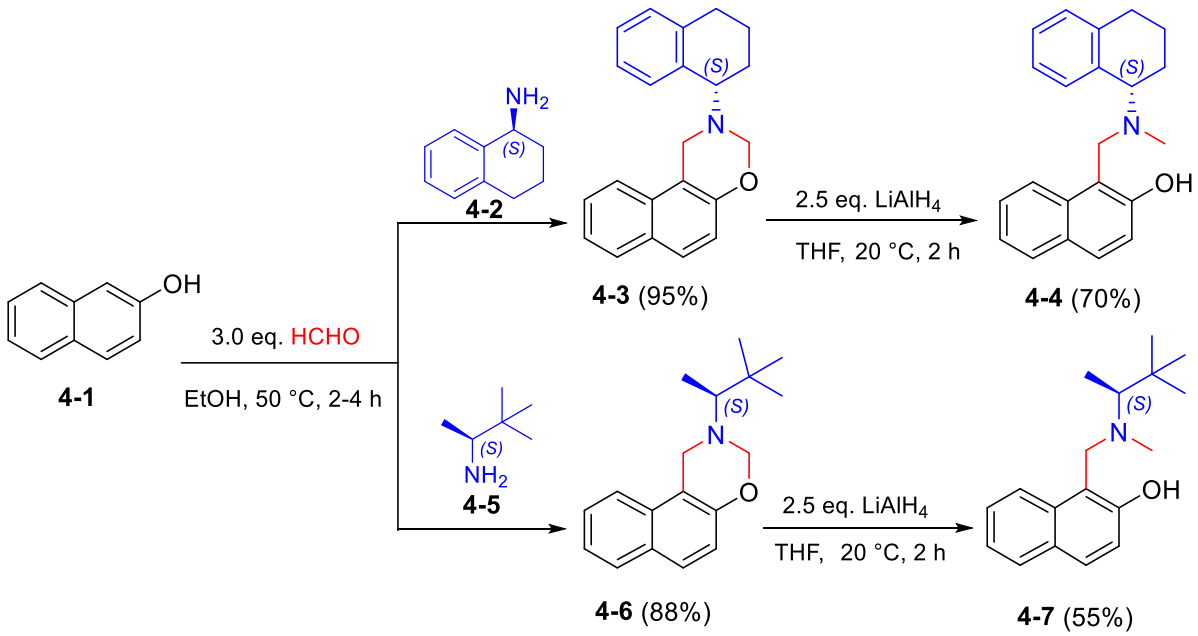
1. Synthesis of dihydro-1,3-naphthoxazines by *Mannich* condensation of naphthalene-2-ol, formaldehyde and chiral amines and their reduction to obtain aminomethylnaphthols with a tertiary amino group.
2. Use of natural amino acid derivatives, such as (*R*)-(–)-2-phenylglycinol and (*R*)-(–)-2-phenylglycine methyl ester, as a source of chirality in *Mannich* condensation.
3. Carrying out *Mannich* condensation to obtain chiral, non-racemic bis-dihydro-1,3-naphthoxazines using enantiomerically pure (*R*,*R*)- or (*S*,*S*)-cyclohexane-1,2-diamine, as well as in the condensation of naphthalenediols with (*S*)-(–)-1-phenylethan-1-amine.
4. *Mannich* condensation of quinolin-6-ol, formaldehyde and chiral amines and subsequent reduction.
5. Carrying out *Betti* condensation of quinolin-6-ol or quinolin-7-ol (quinolin analogues of naphthalene-2-ol) with aromatic aldehydes and chiral amines.
6. Structural characterization of the synthesized new chiral compounds using one-dimensional and two-dimensional NMR spectroscopy, mass spectrometry, specific rotation angle and elemental analysis.
7. Determining the configuration of the newly formed stereogenic center in *Betti* condensation products by applying modern NMR techniques and X-ray structural analysis.
8. Synthesis of structurally diverse compounds using diketopiperazine Cyclo(Gly-Pro) as a basic component in reactions with different electrophiles.
9. Application of the newly obtained enantiomerically pure aminobenzyl-naphthols and -quinolinols as catalysts in a model reaction for the enantioselective addition of diethylzinc to aldehydes.
10. Evaluation of the obtained compounds for antimicrobial and antiviral activity.

# 4. RESULTS AND DISCUSSION

As a continuation of the experiments and the results achieved in the laboratory of "Organic Synthesis and Stereochemistry", in which the current dissertation work was prepared, we focused on the synthesis of new chiral dihydro-1,3-naphthoxazines.

## 4.1. *Mannich* condensation of naphthalen-2-ol (4-1) with formaldehyde and chiral amines to dihydro-1,3-naphthoxazines and their reduction

The condensation of naphthalen-2-ol (**4-1**) with formaldehyde and chiral amines: (*S*)-(+)-1,2,3,4-tetrahydronaphthalen-1-amine (**4-2**) and (*S*)-(+)-3,3-dimethylbutan-2-amine (**4-5**) was carried out in ethanol at 50 °C within 2 to 3 h. Formaldehyde was embedded as formalin (37% aqueous solution) or as paraformaldehyde. Products **4-3** and **4-6** were isolated in pure form after chromatographic purification as colorless amorphous substances in 95% and 88% yields, respectively. The resulting dihydro-1,3-naphthoxazines **4-3** and **4-6** were successfully reduced with $LiAlH_4$ to the corresponding *N*-methyl aminomethylnaphthols **4-4** and **4-7** in 70% and 55% yields, respectively (Scheme **A**).




**Scheme A** Preparation of the *N*-methyl aminomethylnaphthols **4-4** and **4-7** (Scheme **4-3** and Scheme **4-4** summarized)

Aminonaphthol **4-7** was found to be unstable and decomposed upon prolonged standing at room temperature. Store in an argon atmosphere and at a temperature of 4 °C.

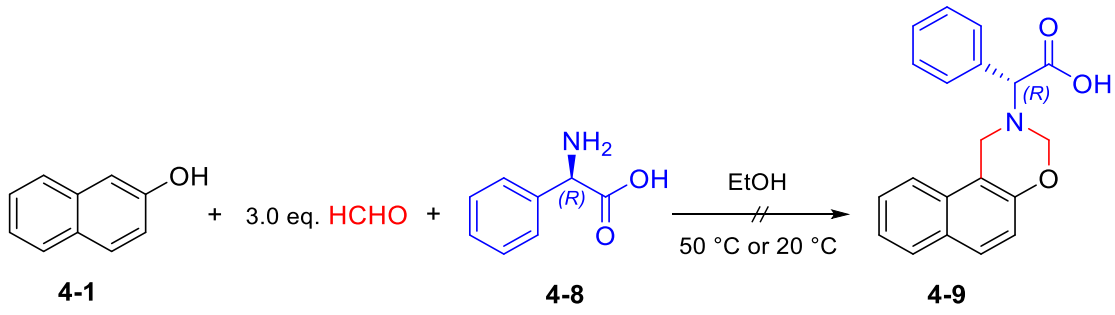
The newly synthesized compounds (**4-3**, **4-4**, **4-6** and **4-7**), after purification by column chromatography, were characterized by $^{1}H$ and $^{13}C$ NMR spectroscopy and two-dimensional spectra: *COSY*, *HSQC*, *HMBC*; mass spectrometry; specific angle of rotation; melting point and elemental analysis. The obtained two-dimensional NMR spectra allow the complete reference of the signals for all protons and carbon atoms.

The effectiveness of aminomethylnaphthols **4-4** and **4-7** as catalysts in enantioselective reactions was tested in an addition reaction of diethylzinc to aromatic aldehydes (section **4.8.**).

## 4.2. *Mannich* condensation of naphthalene-2-ol (4-1) with formaldehyde and chiral derivatives of natural amino acids as the amine component to dihydro-1,3-naphthoxazines and their reduction

Amino acids – natural and synthetic, are readily available commercial products, and due to their chirality, they are suitable for application in asymmetric synthesis. The presence of two functional groups enables further transformations to a variety of new products. This is the reason for their wide application in organic synthesis to obtain new chiral, non-racemic compounds with potential catalytic and biological activity.

In order to obtain new chiral aminomethylnaphthols, (*R*)-(–)-2-phenylglycine (**4-8**) was used in a modified *Mannich* reaction. An attempt to obtain the dihydro-1,3-naphthoxazine **4-9** was unsuccessful (Scheme **4-5**).



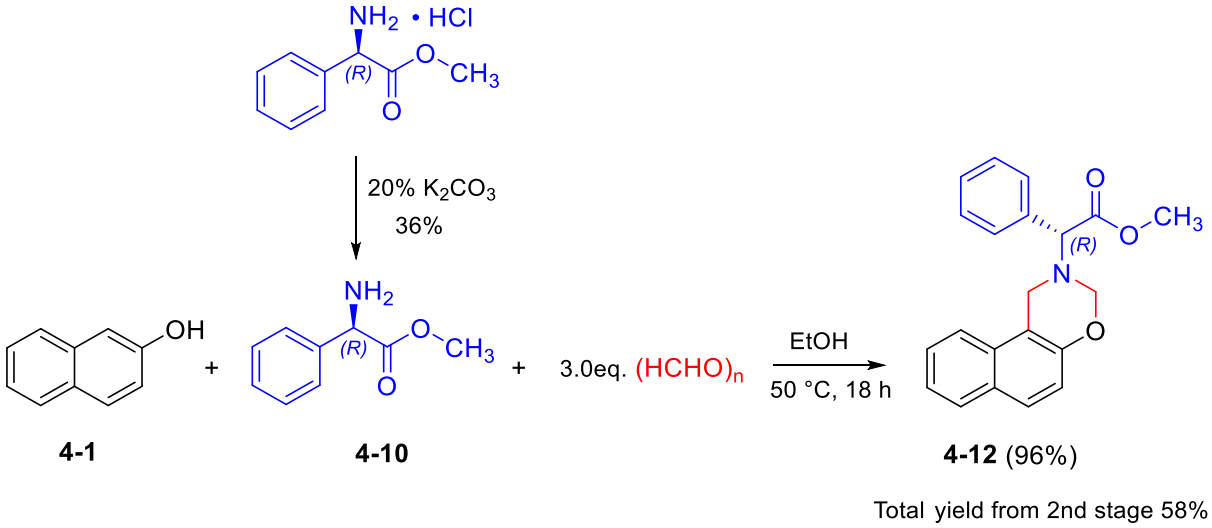

**Scheme 4-5** Condensation of naphthalen-2-ol (**4-1**), formaldehyde and (*R*)-(–)-2-phenylglycine (**4-8**)

The direct use of the amino acid **4-8** in a *Mannich* reaction did not lead to a product, therefore it was necessary to use its derivatives such as the methyl ester of (*R*)-(–)-2-phenylglycine (**4-10**) and (*R*)-(–)-2-phenylglycinol (**4-14**).

### 4.2.1. *Mannich* condensation of naphthalen-2-ol (4-1), paraformaldehyde and methyl ester of *R*-(–)-2-phenylglycine (4-10) and subsequent reduction of the product obtained

The choice of the chiral amino ester **4-10** was dictated by the fact that it is readily available and relatively inexpensive, as well as by the need to compare the results achieved by the group in the *Betti* condensation with those obtained in the *Mannich*.

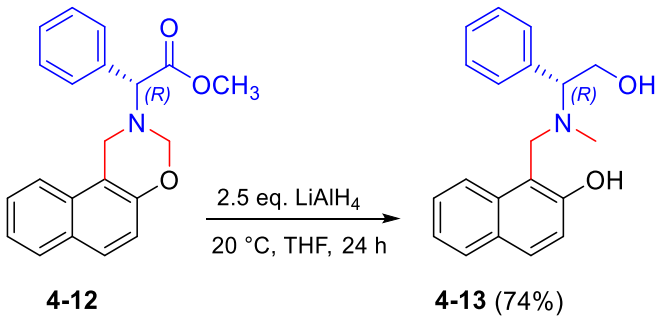
*Mannich* condensation of (*R*)-(–)-2-phenylglycine methyl ester (**4-10**) with naphthalen-2-ol (**4-1**) and paraformaldehyde in ethanol was carried out under heating at 50 °C (Scheme **4-8**).




**Scheme 4-8** Condensation of naphthalene-2-ol (**4-1**), formaldehyde and *R*-(–)-2-phenylglycine methyl ester (**4-10**)

The methyl ester **4-10** is in the form of hydrochloride, and the bases $Et_3N$ and $K_2CO_3$ were used to release it as a free base. Using $Et_3N$ as the base and conducting the reaction in one step, the product **4-12** was obtained in 60% yield. It is possible to carry out the condensation in two stages, as shown in Scheme **4-8**. In the first step, the ester **4-10** was obtained as a free base by treating its hydrochloride with a 20% solution of $K_2CO_3$, where it was isolated with a yield of 36%. In the next step, **4-10** was subjected to a *Mannich* reaction, and the yield of the isolated target product **4-12** was high – 96%. The total yield from the two stages in this case is 58%.

In the reduction of **4-12** with $LiAlH_4$, the *N*-methylated product **4-13** was obtained, and in the course of the reaction, the ester group and the oxazine ring were simultaneously reduced (Scheme **4-9**). After purification by column chromatography, the product **4-13** was isolated in pure form in 74% yield.




**4-12** **4-13** (74%)

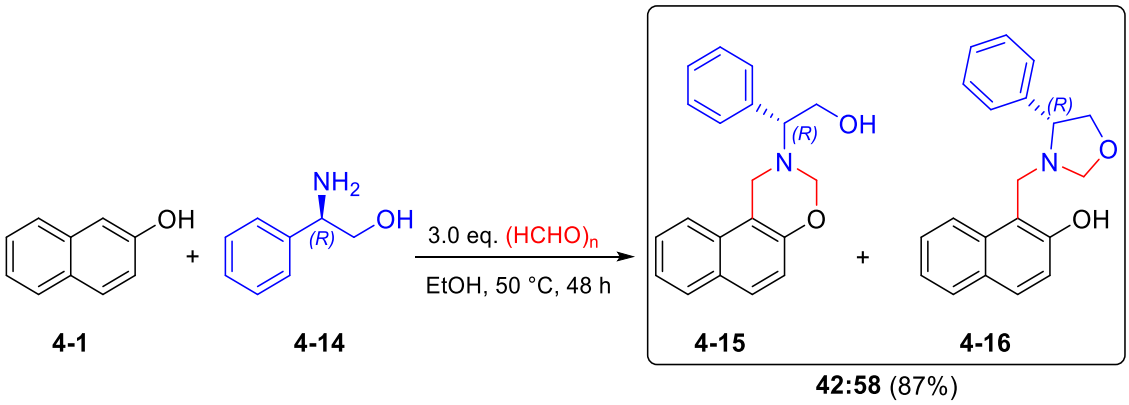
**Scheme 4-9** Preparation of *N*-methyl aminomethylnaphthol **4-13**

The rotation angle of **4-13** was determined using a polarimeter: $[\alpha]_D^{20} = -14$ (c 1, $CHCl_3$). The fact that a rotation angle was measured for compound **4-13** indicates that the product obtained is optically active, but does not prove whether, in the course of preparation of **4-12**, partial racemization does not occur at the C-atom attached to the amino group of the phenylglycine fragment. Such racemization was observed using (*R*)-(–)-2-phenylglycine methyl ester (**4-10**) in *Betti* condensation with naphthalene-2-ol (**4-1**) and 1-naphthaldehyde.

In order to prove with certainty that *N*-methyl aminomethylnaphthol **4-13**, obtained by the methods described in Scheme **4-8** and Scheme **4-9**, is a pure enantiomer, a new approach was chosen for its preparation, described in section **4.2.2.**

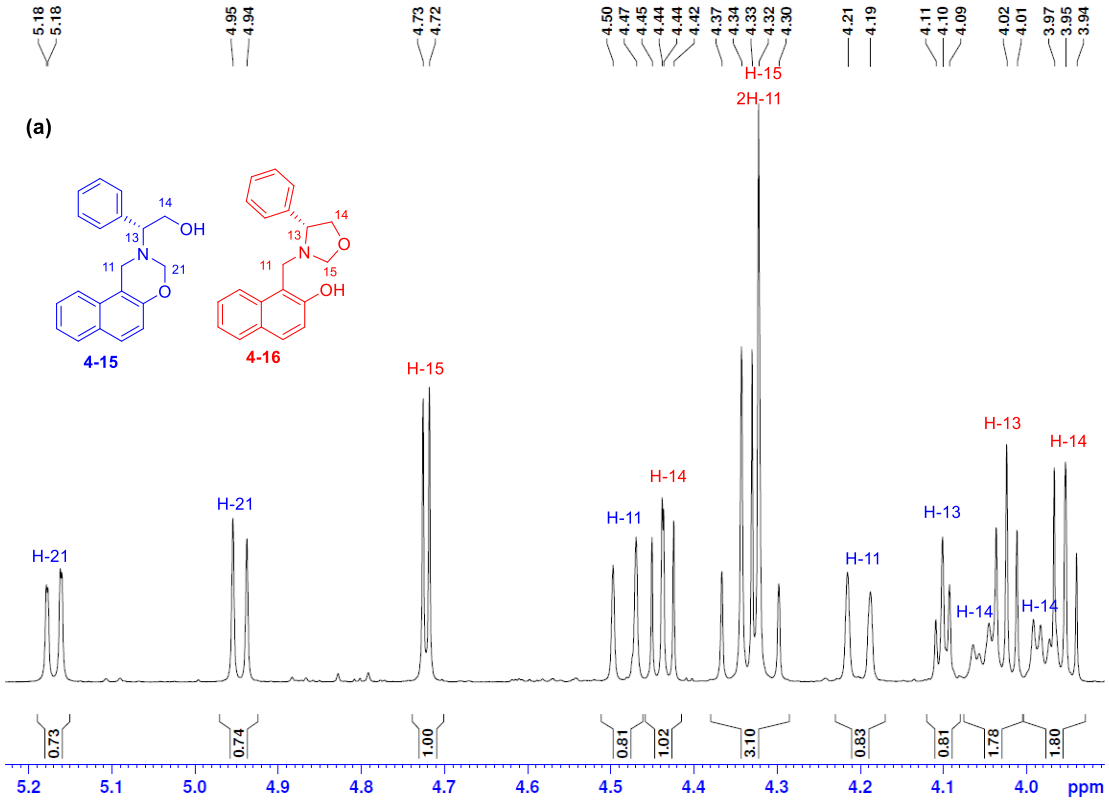
### 4.2.2. *Mannich* condensation of naphthalen-2-ol (4-1), paraformaldehyde and (*R*)-(–)-2-phenylglycinol (4-14) and subsequent reduction of the product

The condensation of (*R*)-(–)-2-phenylglycinol (**4-14**) with naphthalen-2-ol (**4-1**) and paraformaldehyde gave a mixture of two products **4-15** and **4-16** in a ratio of 42:58 (according to $^1H$ NMR data), in an overall yield of 87%, determined after purification of the reaction mixture by column chromatography (Scheme **4-10**).




**Scheme 4-10** Condensation of naphthalene-2-ol (**4-1**), paraformaldehyde and (*R*)-(–)-phenylglycinol (**4-14**)

Attempts to separate the two products by column chromatography or recrystallization were unsuccessful. Using $^{1}H$ and $^{13}C$ NMR spectroscopy and two-dimensional spectra (*COSY*, *HSQC*, *HMBC*), the structure of the two products was determined. Figure **4-1** shows **a**) the $^{1}H$ NMR spectrum of a 42:58 mixture of **4-15** and **4-16** and **b**) the *HSQC* spectrum of the same mixture, and Table **4-1** gives some characteristic proton chemical shifts and C atoms at **4-15** and **4-16**.



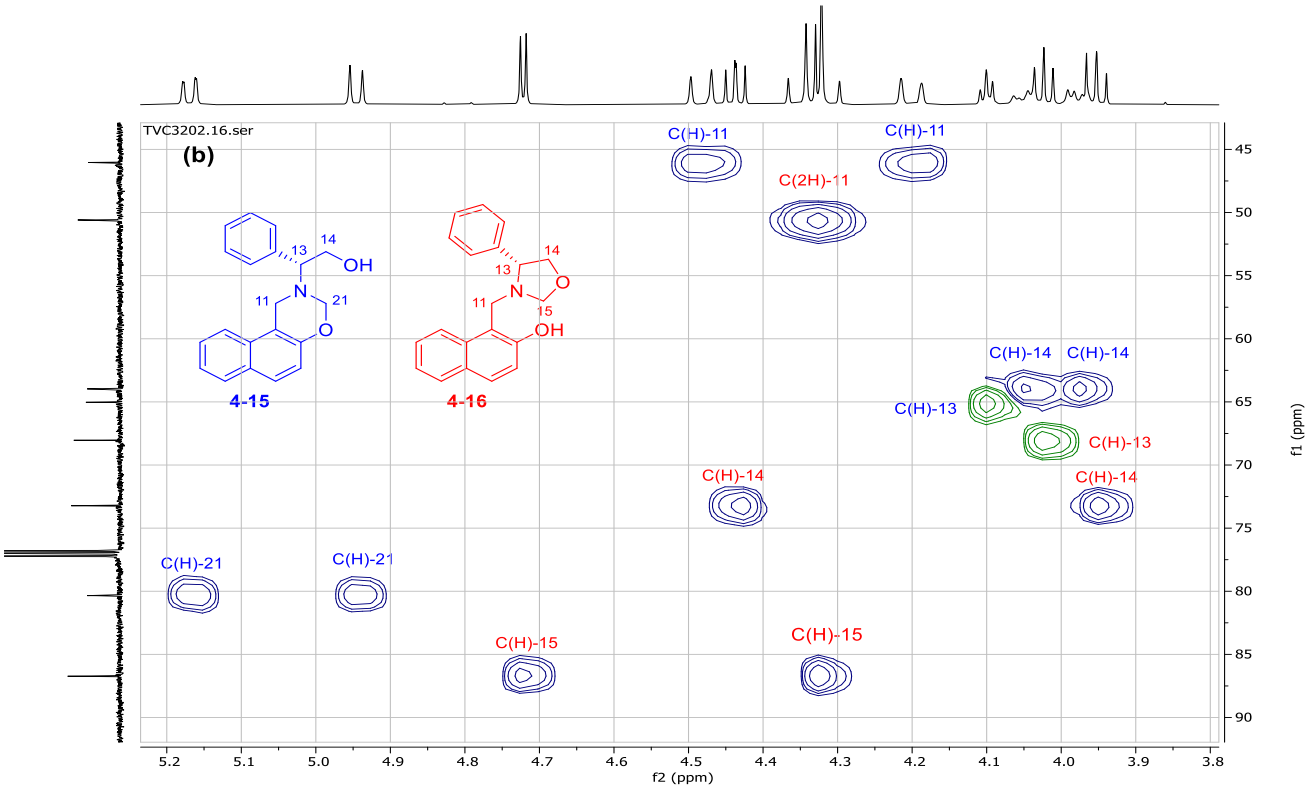
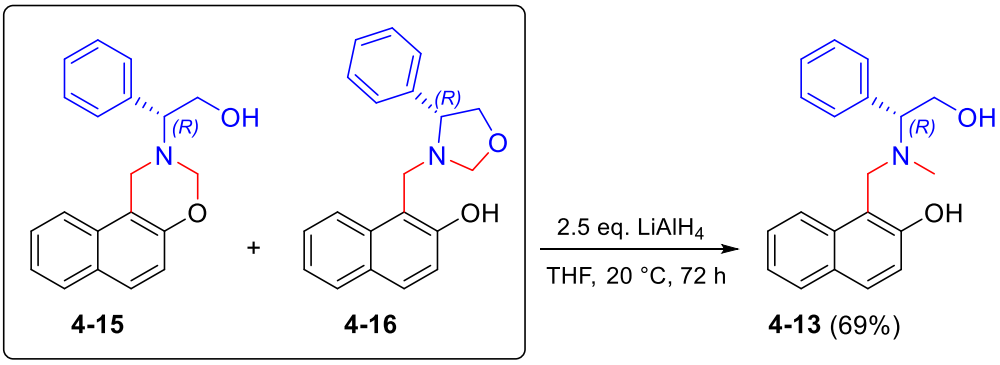



**Figure 4-1** Aliphatic region of **a**) $^{1}$H NMR spectrum, **b**) *HSQC* spectrum of a 42:58 mixture of **4-15** and **4-16** with assigned chemical shifts

**Table 4-1** Chemical shifts (in ppm) and spin interaction constants for the aliphatic protons and carbon atoms in the NMR spectra of compounds **4-15** and **4-16**

| **Number of C-atom in the skeleton** | **4-15** | | **4-16** | |
|---|---|---|---|---|
| | $\delta^{1}$H, multiplicity (*J* in Hz) | $\delta^{13}$C | $\delta^{1}$H, multiplicity (*J* in Hz) | $\delta^{13}$C |
| C(H)-11 | 4.20, d (16.6)<br>4.48, d (16.6) | 46.03 | 4.31, d (14.1)<br>4.35, d (14.1) | 50.59 |
| C(H)-13 | 4.10, t (4.9) | 65.03 | 4.02, t (15.0) | 69.04 |
| C(H)-14 | 3.98, dd (11.5, 5.1)<br>4.05, dd (11.5, 4.5) | 63.97 | 3.96, t (8.2)<br>4.44 dd (8.4, 7.3) | 73.22 |
| C(H)-15 | – | – | 4.35, d (4.6)<br>4.72, d (4.6) | 86.73 |
| C(H)-21 | 4.95, d (10.1)<br>5.17, dd (10.1, 1.2) | 80.34 | – | – |

The mixture of **4-15** and **4-16** was subjected to reduction with $LiAlH_4$, where the aminodiol **4-13** was isolated in 69% yield after purification by column chromatography (Scheme **4-11**). The thus obtained product **4-13** was characterized by NMR spectroscopy and was identical to the product obtained after reduction of dihydro-1,3-naphthoxazine **4-12** (Section **4.2.1.**).




**Scheme 4-11** Preparation of compound **4-13** after reduction of the mixture of **4-15** and **4-16**

The measured rotation angle (under the same conditions) has the same value as that of the product obtained by the method described in section **4.2.1.**, namely $[\alpha]_D^{20} = -13.6$ (c 1.15, $CHCl_3$). This proves that in the *Mannich* condensation of methyl ester of (*R*)-(–)-2-phenylglycine (**4-10**) (section **4.2.1.**) or (*R*)-(–)-2-phenylglycinol (**4-14**), as sources of chirality, with naphthalen-2-ol (**4-1**) and paraformaldehyde, there is no loss of chiral information.

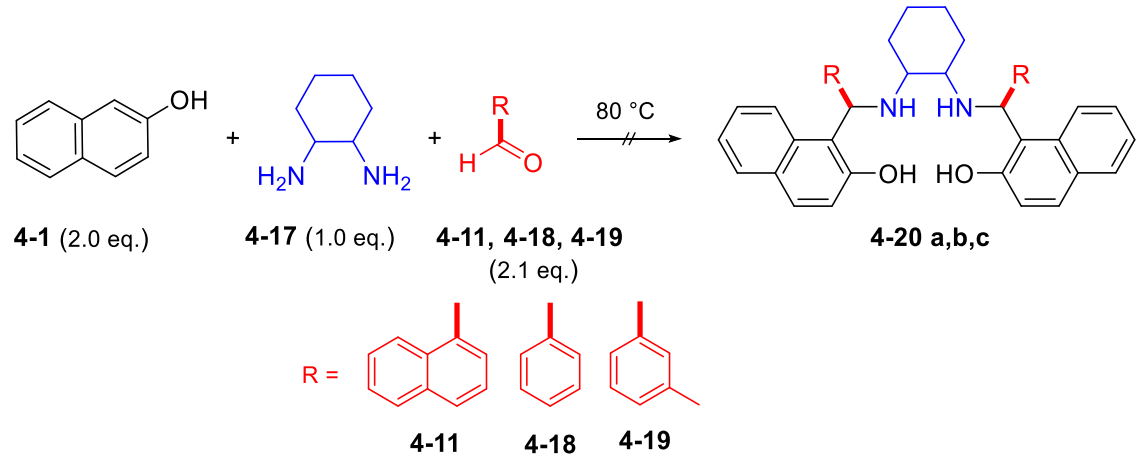
The aminodiol **4-13** finds application as a ligand in enantioselective addition reactions of diethylzinc to aldehydes (Section **4.8.**).

## 4.3. Condensation of naphthalen-2-ol with cyclohexane-1,2-diamine and aldehydes

Only single examples of the preparation of aminonaphthols with $C_2$-symmetry are described in the literature. This sparked our interest in conducting a *Mannich* reaction with cyclohexane-1,2-diamine, which possesses such symmetry, is readily available, and at relatively low cost. On the other hand, ligands whose structures are built from a *β*-aminonaphthol and/or from a *trans*-cyclohexane-1,2-diamine moiety are widely used as catalysts in the asymmetric addition of dialkylzinc to carbonyl compounds

### 4.3.1. *Betti* condensation of naphthalen-2-ol (4-1), aromatic aldehydes and cyclohexane-1,2-diamine (4-17)

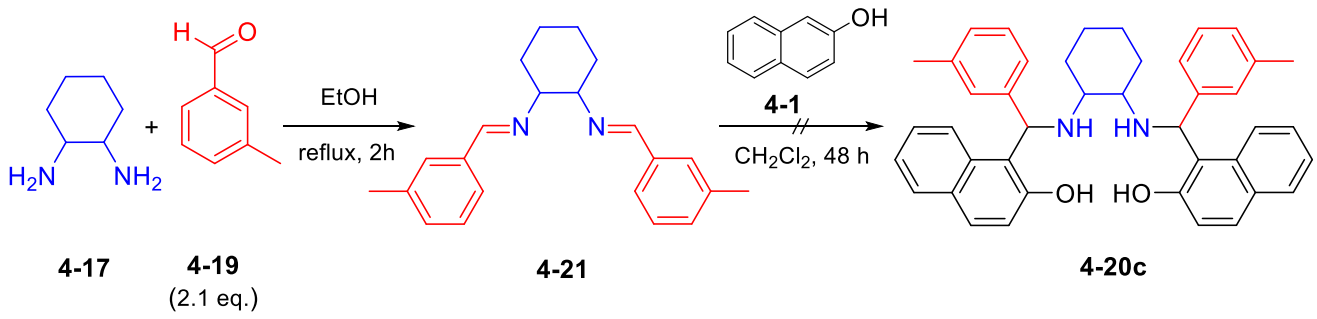
In order to obtain bis-aminobenzylnaphthols of the type **4-20**, initially *Betti* condensations were carried out between cyclohexane-1,2-diamine (**4-17**), in the form of racemate, and naphthalen-2-ol (**4-1**) with different aromatic aldehydes – 1-naphthaldehyde (**4-11**), benzaldehyde (**4-18**), and 3-methyl-benzaldehyde (**4-19**). (Scheme **4-12**).




**Scheme 4-12** General procedure for the preparation of bis-aminobenzylnaphthols of type **4-20** by *Betti* condensation

The progress of the reaction was monitored by thin-layer chromatography, with some decomposition of the starting compounds being recorded over time, as well as the absence of a defined product spot.

Attempts were made to carry out the reaction in two steps, the first being the preparation of an imine from an aldehyde, in this case 3-methylbenzaldehyde (**4-19**) and **4-17** (Scheme **4-13**).




**Scheme 4-13** Synthesis of bis-aminobenzylnaphthol **4-20c** in two steps

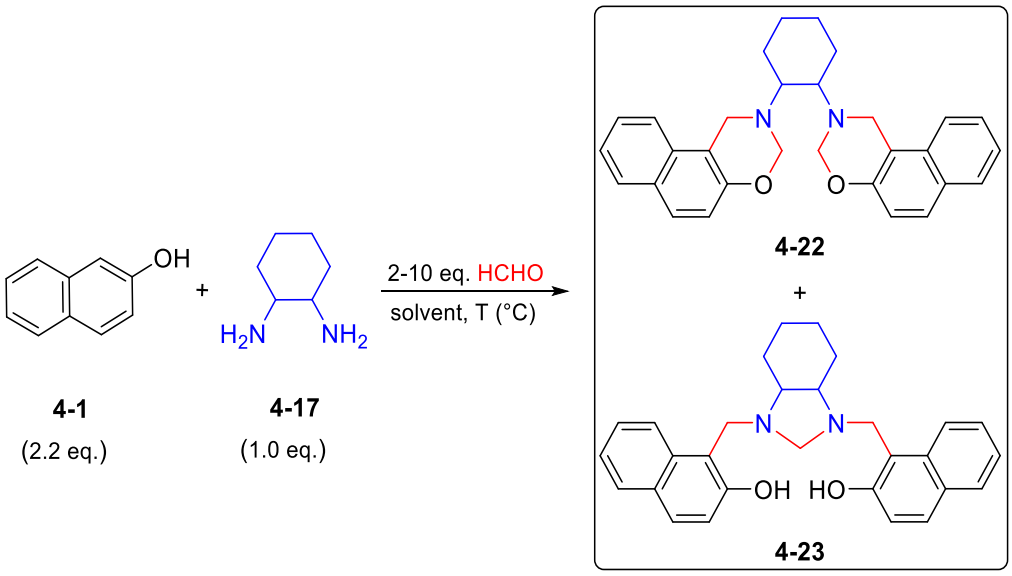
After 2 hours of boiling in ethanol, $^{1}$H NMR spectrum of the crude mixture revealed the formation of diimine **4-21**. The second step reaction of **4-21** (without isolation of the diimine) with naphthalen-2-ol (**4-1**) did not lead to the target product **4-20c**.

### 4.3.2. *Mannich* condensation of naphthalen-2-ol (4-1), formaldehyde and cyclohexane-1,2-diamine (4-17) in racemate form

After unsuccessful attempts to directly prepare bis-aminobenzylnaphthols by *Betti* condensation with aromatic aldehydes, we turned to *Mannich* condensation with formaldehyde. The initial aim was the preparation of bis-dihydro-1,3-naphthoxazines of the type **4-22**, whose reduction in a subsequent step would lead to the preparation of the target bis-*N*-methyl-aminomethylnaphthols.

A series of reactions of cyclohexane-1,2-diamine (**4-17**) (as the racemate) and naphthalen-2-ol (**4-1**) with formaldehyde were carried out (Table **4-2**). From $^{1}$H NMR spectra of the crude reaction mixture, the presence of two products **4-22** and **4-23** was determined in different ratio depending on the reaction conditions. Attempts to separate and isolate the products in pure form have been unsuccessful. After optimizing the conditions for the preferred preparation of **4-22**, it was found that when the reaction was carried out in toluene at 50 °C (row 8), the products **4-22** and **4-23** were formed in a ratio of 1:02, which was the most the good ratio in favor of **4-22**.

**Table 4-2** Optimizing reaction conditions for condensation of naphthalen-2-ol (**4-1**), formaldehyde and 1,2-cyclohexanediamine (**4-17**)



| № | HCHO (eq.) | Solvent | Time (h) | T (°C) | Mole ratio 4-22:4-23[c] | Yield[e] 4-23 (%) |
|---|---|---|---|---|---|---|
| 1 | 10[a] | EtOH | 3 | 20 | 1:0.4 | - |
| 2 | 10[a] | EtOH | 5 | 20 | 1:0.5 | - |
| 3 | 10[a] | EtOH | 1 | 50 | 1:0.4 | - |
| 4 | 10[a] | EtOH | 6 | 50 | 1:0.5 | - |
| 5 | 10[a] | EtOH | 18 | 50 | 1:0.95[d] | - |
| 6 | 10[b] | EtOH | 24 | 50 | 0.7:1 | 34[f] |
| 7 | 10[a] | EtOH | 2.5 | reflux | 0.4:1 | - |
| 8 | 10[b] | толуен | 24 | 50 | 1:0.2 | - |
| 9 | 4[a] | dioxane | 1 | 20 | 0.4:1 | - |
| 10 | 2[a] | MeOH | 2 | reflux | 0:1 | 50[g] |
| 11 | 2[b] | MeOH | 2 | reflux | 0:1 | 46[g] |
| 12 | 2[b] | EtOH | 2 | reflux | 0:1 | 34[g] |
| 13 | 2[b] | EtOH | 24 | 50 | 0:1 | 63[f] |

[a]37% aqueous solution of formaldehyde
[b]Paraformaldehyde
[c]Mole ratio determined by $^1$H NMR spectroscopy of crude mixture
[d]The ratio was determined after washing the crude reaction mixture with acetonitrile
[e]Yield isolated compounds
[f]Yield of **4-23** determined after column chromatography
[g]Yield**,** determined after filtering the crystallized **4-23** from the reaction mixture

In a search for conditions to preferentially prepare bis-dihydro-1,3-naphthoxazine **4-22**, those were found to give only product **4-23** when the reaction was carried out in EtOH at 50 °C for 24 h. Under these conditions, **4-23** was obtained in 63% yield.

When comparing the $^1$H NMR spectra of the pure product **4-23** (**c**) in Figure **4-2**) with those of an isolated mixture of **4-22** and **4-23** ((**a**) in Figure **4-2**) and of a predominant **4-22** ((**b**) in Figure **4-2**), it is possible to determine the characteristic signals for the two products, with significant differences in the chemical shifts observed for C(H)-11, C(H)-13, and C(H)-16. Thus, without isolation, it is possible to distinguish the two compounds in a mixture and unambiguously determine their structures using NMR and HRMS experiments.

The characteristic chemical shifts of both compounds **4-22** and **4-23** for C(H)-11, C(H)-13, and C(H)-16 are shown in Table **4-3**.

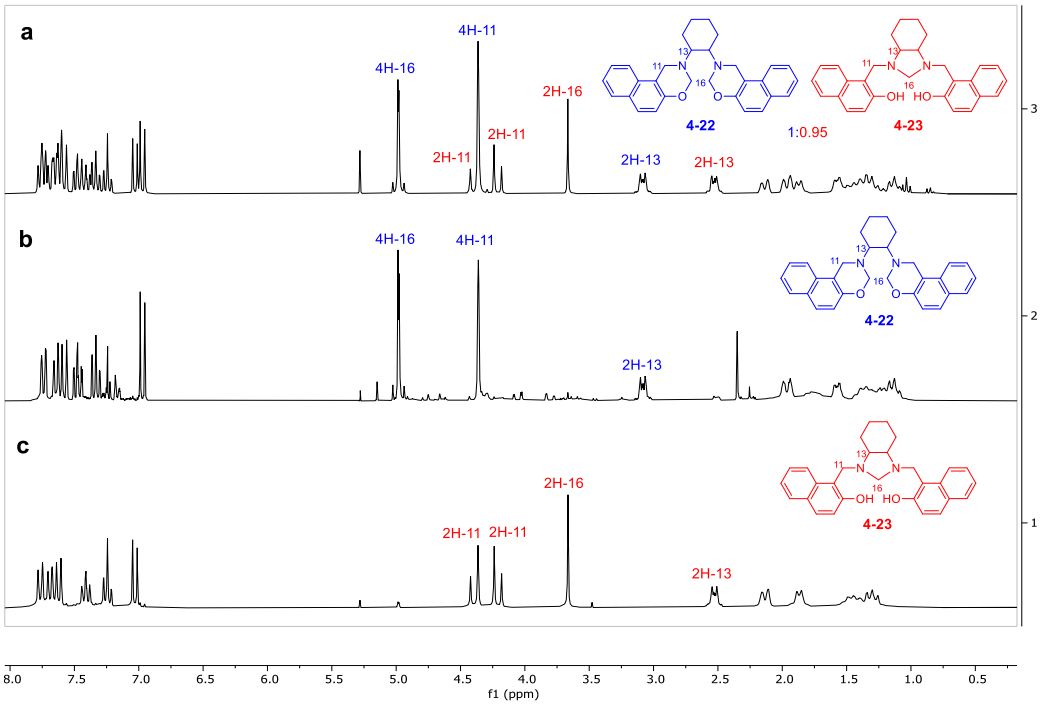
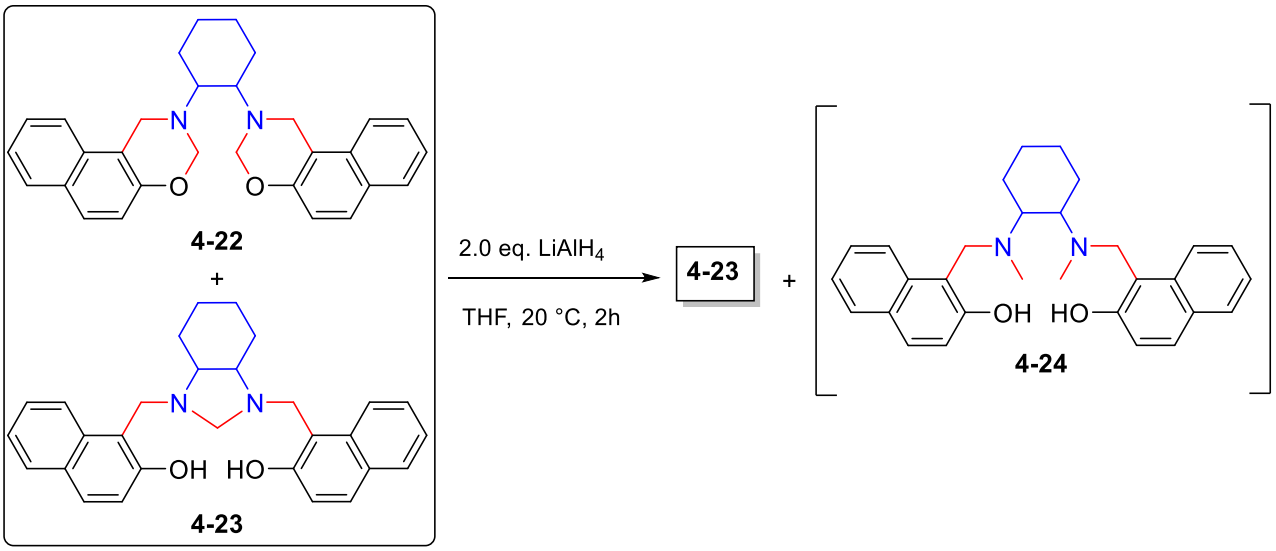



**Figure 4-2** $^{1}$H NMR spectra of: (**a**) mixture of **4-22** and **4-23** (1:0.95); (**b**) crude product **4-22** and (**c**) pure product 4-**23** with characteristic chemical shifts indicated (in ppm)

**Table 4-3** Data on characteristic chemical shifts (in ppm) of selected protons, allowing to distinguish compounds **4-22** and **4-23** in a mixture

| **Characteristic protons** | **4-22** | **4-23** |
|---|---|---|
| | $^{1}$H-NMR (number of protons) | $^{1}$H-NMR (number of protons) |
| C(H)-11 | 4.36 (4H) | 4.21 (2H)<br>4.39 (2H) |
| C(H)-13 | 3.03-3.14 (2H) | 2.47-2.58 (2H) |
| C(H)-16 | 4.96 (2H)<br>5.01 (2H) | 3.66 (2H) |

As mentioned, the two products **4-22** and **4-23** cannot be separated and isolated in pure form. Therefore, the resulting mixture of the two compounds, in a ratio of 1:1, was subjected to reduction with $LiAlH_4$ in order to obtain the *N*,*N*-dimethyl derivative **4-24**. The reaction was carried out at 20 °C in THF for 2 h (Scheme **4-15**).



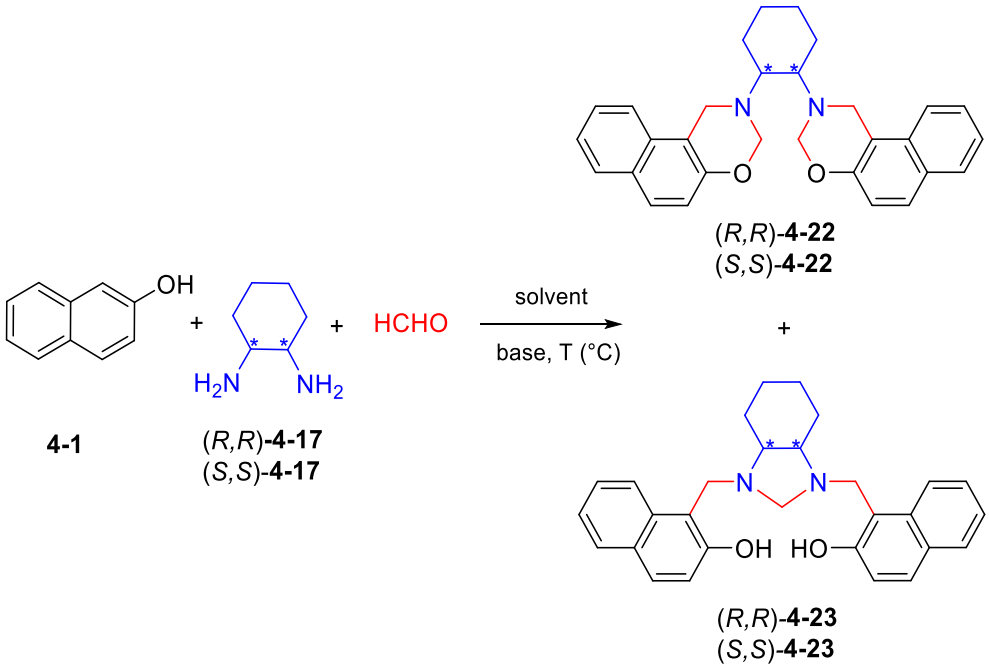

**Scheme 4-15** Reduction of a 1:1 mixture of **4-22** and **4-23** with $LiAlH_4$

The $^1H$ NMR spectrum of the crude reaction mixture revealed the presence of **4-23**. The characteristic signals of **4-22** are missing, which means that decomposition of this compound occurred in the course of the reaction. After column chromatography, no product designated **4-24** was isolated. The reduction with $NaBH_4$ was also unsuccessful.

### 4.3.3. *Mannich* condensation of naphthalene-2-ol (4-1), formaldehyde and (*R*,*R*)- or (*S*,*S*)-cyclohexane-1,2-diamine (4-17)

In parallel with the optimization of the conditions for the preparation of **4-22** and **4-23** from racemic cyclohexane-1,2-diamine (**4-17**), a *Mannich* condensation of enantiomerically pure (*R*,*R*)- or (*S*,*S*)-cyclohexane-1,2-diamine ((*R*,*R*)-**4-17** or (*S*,*S*)-**4-17**, respectively) with naphthalen-2-ol (**4-1**) and formaldehyde, in order to obtain chiral non-racemic ligands of suitable structure in relation to their application in asymmetric catalysis. Condensation of (*R*,*R*)-**4-17** with naphthalen-2-ol (**4-1**) and formaldehyde (10.0 equiv) isolated a mixture of bis-dihydro-1,3-naphthoxazine (*R*,*R*)-**4-22** and imidazolidine product (*R*,*R*)-**4-23**, and using (*S*,*S*)-**4-17** a mixture of bis-dihydro-1,3-naphthoxazine (*S*,*S*)-**4-22** was isolated and imidazolidine product (*S*,*S*)-**4-23**. The molar ratio of the products in the isolated mixtures as well as the yield of imidazolidine (*R*,*R*)-**4-23** and (*S*,*S*)-**4-23** in these mixtures were determined based on the integrals of characteristic protons in the $^1H$ NMR spectrum of the mixture (Table **4-4**).

**Table 4-4** Optimization of reaction conditions for the condensation of 2-naphthol (**4-1**), formaldehyde and (*R*,*R*)- or (*S*,*S*)-cyclohexane-1,2-diamine ((*R*,*R*)-**4-17**, (*S*,*S*)-**4-17**, respectively)

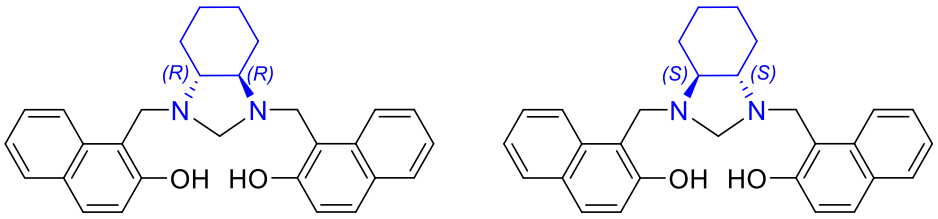



**4-1** (*R*,*R*)-**4-17** (*S*,*S*)-**4-17** (*R*,*R*)-**4-22** (*S*,*S*)-**4-22** (*R*,*R*)-**4-23** (*S*,*S*)-**4-23**

| № | HCHO (eq.) | *(R,R)*- or *(S,S)*-diamine | Base | Solvent | Time (h) | T (°C) | Mole ratio 4-22:4-23[e] | Yield 4-23 (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | 10[a] | (*R*,*R*)-**4-17**[c] | $Et_3N$ | EtOH | 24 | кипене | 0.5:1 | 22[f] |
| 2 | 10[a] | (*R*,*R*)-**4-17**[c] | KOH | EtOH | 24 | кипене | 1:0.5 | 9[f] |
| 3 | 10[a] | (*R*,*R*)-**4-17**[c] | $K_2CO_3$ | EtOH | 24 | кипене | 0.2:1 | 24[f] |
| 4 | 10[a] | (*S*,*S*)-**4-17**[c] | $K_2CO_3$ | EtOH | 24 | кипене | 0.4:1 | 24[g] |
| 5 | 2[a] | (*R*,*R*)-**4-17**[c] | $K_2CO_3$ | EtOH | 24 | 50 | 0:1 | 29[f] |
| 6 | 2[b] | (*R*,*R*)-**4-17**[c] | $K_2CO_3$ | EtOH | 24 | 50 | 0:1 | 30[f] |
| 7 | 2[b] | (*S*,*S*)-**4-17**[c] | $K_2CO_3$ | EtOH | 24 | 50 | 0:1 | 31[g] |
| 8 | 2[b] | (*R*,*R*)-**4-17**[c] | $K_2CO_3$ | MeOH | 2 | кипене | 0:1 | 42[h] |
| 9 | 2[b] | (*R*,*R*)-**4-17**[d] | - | MeOH | 2 | кипене | 0:1 | 47[h] |

[a]37% aqueous solution of formaldehyde
[b]Paraformaldehyde
[c](*R*,*R*)- and (*S*,*S*)-cyclohexane-1,2-diamine is in the tartrate form
[d](*R*,*R*)-cyclohexane-1,2-diamine is as the free base
[e]Mole ratio determined by $^1$H NMR spectroscopy of crude mixture
[f]Yield of (*R*,*R*)-**4-23**, isolated after purification by column chromatography
[g]Yield of (*S*,*S*)-**4-23**, isolated after purification by column chromatography
[h]Yield of (*R*,*R*)-**4-23** determined after filtering the crystallized **4-23** from the reaction mixture.

After finding conditions to obtain racemic **4-23** as the only product in a good yield of 63% (section **4.3.2.**), our interest turned to the synthesis of an enantiomerically pure imidazolidine product.




(*R*,*R*)-**4-23** (*S*,*S*)-**4-23**

**Figure 4-3** Structural formulas of (*R*,*R*)-**4-23** and (*S*,*S*)-**4-23**

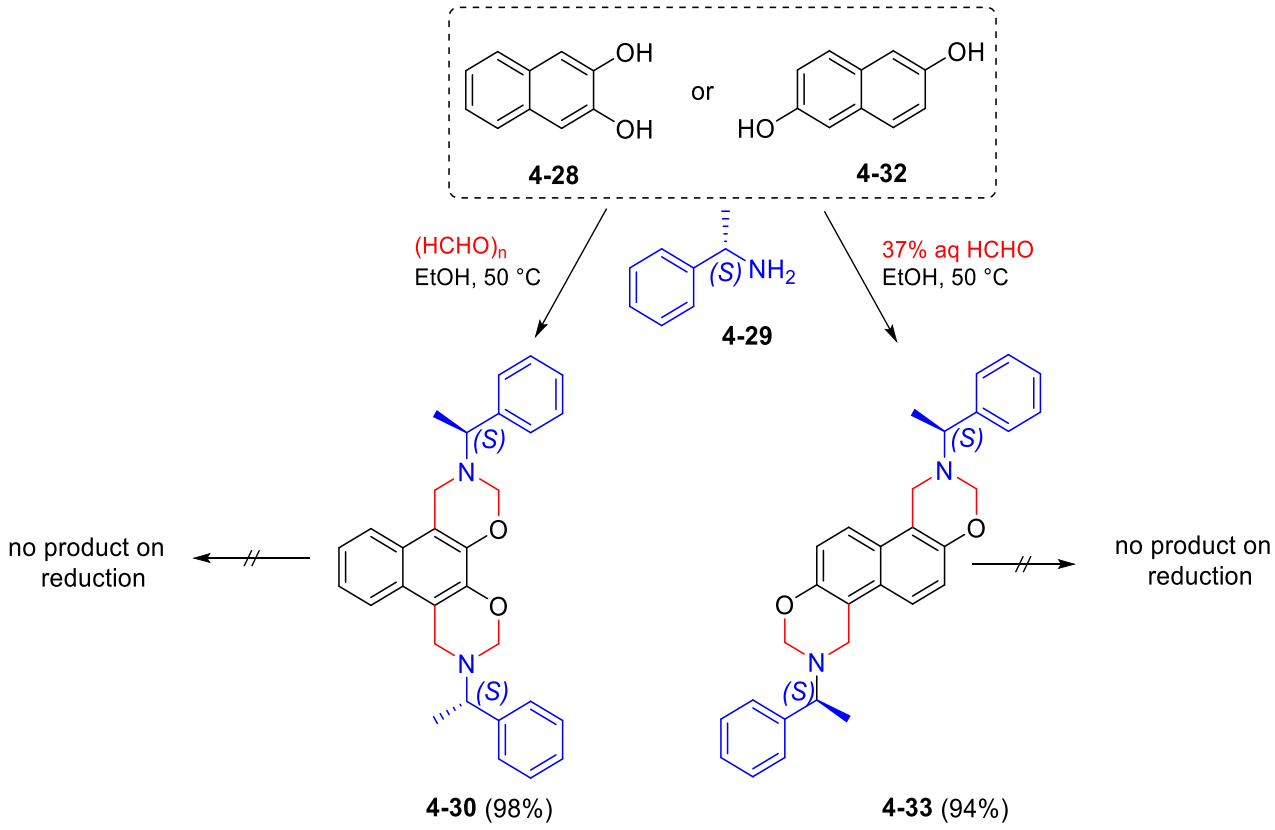
When carrying out the reaction with 2.0 equiv. paraformaldehyde and boiling for 2 h in MeOH as solvent, (*R*,*R*)-**4-23** was isolated in 42% yield (Table **4-4**, row 8). And when the diamine (*R*,*R*)-**4-17** was used as the free base, the yield of the product was increased to 47%, being isolated in high purity (Table **4-4**, row 9). The corresponding enantiomer (*S*,*S*)-**4-23** was obtained in the highest yield of 31% by heating (*S*,*S*)-**4-17** in EtOH at 50 °C (Table **4-4**, row 7).

The isolated compounds (*R*,*R*)-**4-23** and (*S*,*S*)-**4-23** (Figure **4-3**) have not been described in the chemical literature and have been fully characterized by modern analytical methods. The absolute configuration of product (*R*,*R*)-**4-23** was determined by single crystal X-ray diffraction analysis. These imidazolidine derivatives possess suitable structure and properties allowing them to be used as ligands in the model reaction for the enantioselective addition of diethylzinc to aldehydes (Section **4.8.**).

## 4.5. *Mannich* condensation of naphthalenediols with formaldehyde and (*S*)-(−)-1-phenylethan-1-amine and subsequent reduction

Dimitrov's group reported results on the applicability of naphthalene-2,3- and naphthalene-2,6-diols in a condensation reaction with aromatic aldehydes and (*S*)-(−)-1-phenylethan-1-amine (**4-29**). As a continuation of these studies, the bis-dihydro-1,3-naphthoxazines **4-30** and **4-33** were synthesized, in whose reduction, by analogy with the examples in section **4.1.**, the preparation of *N*-substituted bis-aminomethylnaphthols is expected. The interest in carrying out *Mannich* condensation with naphthalenediols is mainly justified by the possibility of realizing a "double" condensation within a dihydroxynaphthol unit, in which to synthesize ligands with two coordination centers, as well as to study the influence of similar structures on the catalytic activity and the degree of asymmetric induction of the ligand. Products **4-30** and **4-33** are obtained by condensation of

naphthalene-2,3-diol (**4-28**) or naphthalene-2,6-diol (**4-32**), formaldehyde and (*S*)-(−)-1-phenylethan-1-amine (**4-29**) and were isolated in high yields of 98% and 94%, respectively (Scheme **B**).




**Scheme B** Condensation of naphthalene-2,3-diol (**4-28**) or naphthalene-2,6-diol (**4-32**), formaldehyde and (*S*)-(−)-1-phenylethan-1-amine (**4-29**)
(Summary Scheme **4-21**, Scheme **4-22**, Scheme **4-23** and Scheme **4-24**)

In the next step, **4-30** and **4-33** were subjected to reduction with $LiAlH_4$ or $NaBH_4$ in order to obtain *N*-substituted bis-aminomethylnaphthols with a tertiary amino group. Carrying out the reaction under different conditions did not lead to the isolation of a defined product.

The structure of product **4-30** as well as the absolute configuration of the stereogenic centers was confirmed by single crystal X-ray diffraction analysis.

## 4.6. Condensation of quinolinols with aldehydes and chiral amines

Condensation of quinolinols with aromatic aldehydes and chiral amines was carried out, and the influence of the quinolinol component on the course of the condensation, as well as on the catalytic

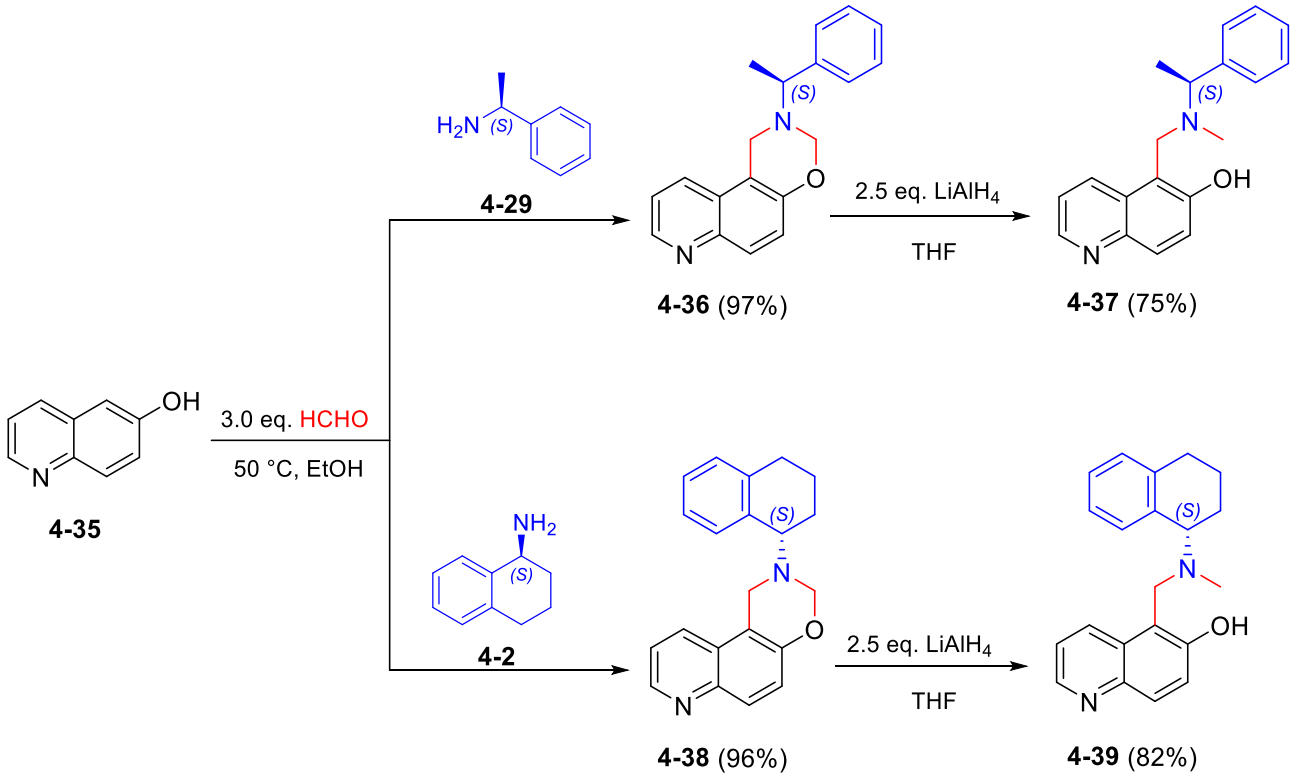
activity of the obtained aminoquinolinols in addition reactions of dialkylzinc compounds to aldehydes, was investigated.

### 4.6.1. *Mannich* condensation of quinolin-6-ol (4-35), formaldehyde and chiral amines to dihydro-1,3-oxazinquinolines and their reduction to aminomethylquinolinols

Dihydro-1,3-oxaziniquinolines **4-36** and **4-38** were synthesized by condensation of formaldehyde with the chiral amines (*S*)-(−)-1-phenylethan-1-amine (**4-29**) or (*S*)-(+)-1,2,3,4-tetrahydronaphthalen-1-amine (**4-2**) and the electron-rich component quinolin-6-ol (**4-35**) (Scheme **4-25**). The reactions were carried out under heating at 50 °C in an ethanol medium in the presence of 37% aqueous formaldehyde or paraformaldehyde.

Dihydro-1,3-oxazinoquinolines **4-36** and **4-38** were obtained in high yield above 95%, after purification by column chromatography. In order to obtain chiral amino alcohols bearing a tertiary amino group, **4-36** and **4-38** were reduced with $LiAlH_4$ (Scheme **4-25**). Products **4-37** and **4-39** were obtained in pure form after purification by column chromatography in high yields of 75% and 82%, respectively.

The newly synthesized compounds **4-36**, **4-37**, **4-38** and **4-39** were characterized by $^{1}H$ and $^{13}C$ NMR spectroscopy, mass spectrometry, specific rotation angle, melting point and elemental analysis. The obtained two-dimensional NMR spectra allow the complete reference of the signals for all protons and carbon atoms.

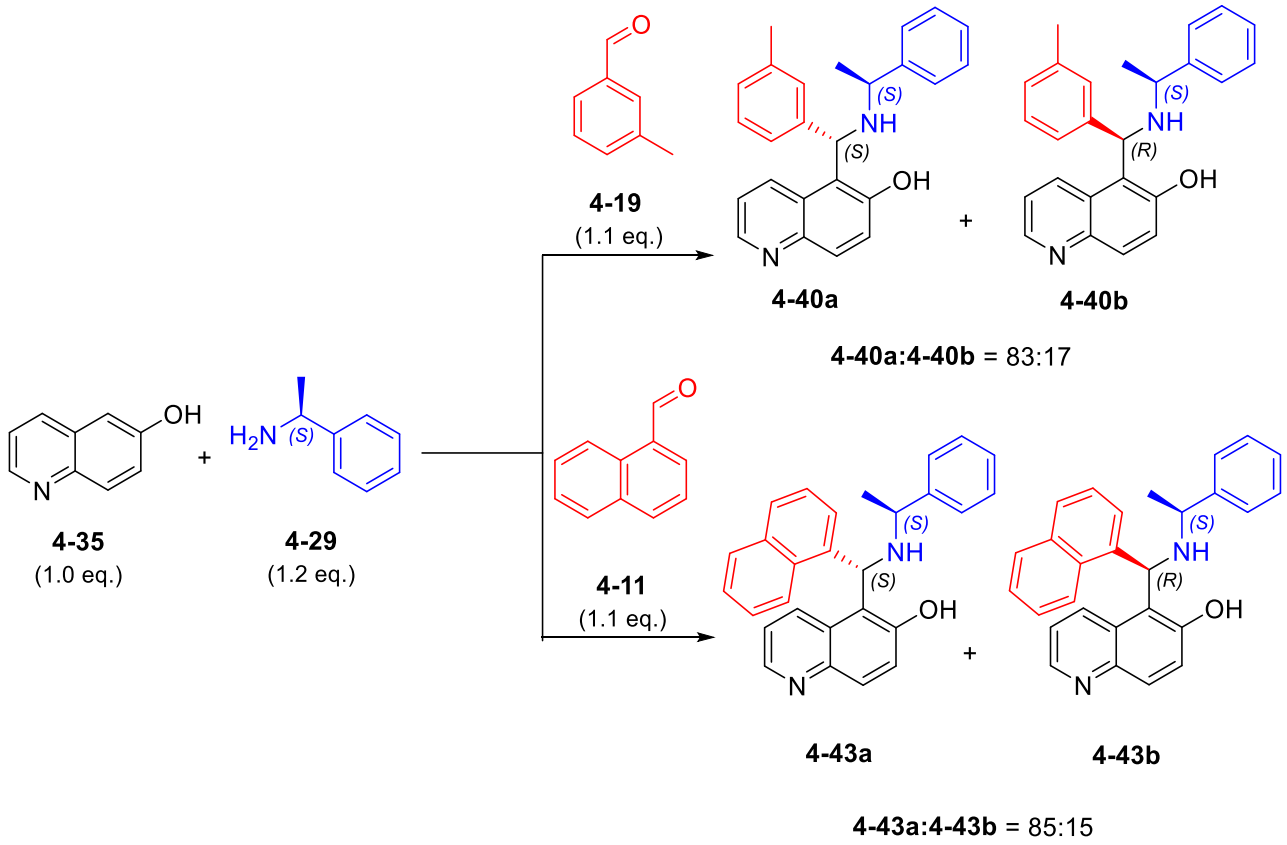



**Scheme 4-25** Condensation of quinolin-6-ol (**4-35**), formaldehyde and chiral aromatic amines. Reduction of dihydro-1,3-oxazinquinolines **4-36** and **4-38**

Chiral aminomethylquinolinols **4-37** and **4-39** were inserted as ligands in the addition of $Et_2Zn$ to aldehydes and their catalytic activity was investigated (Section **4.8.**).

### 4.6.2. *Betti* condensation of quinolin-6-ol (4-35) with 3-methylbenzaldehyde (4-19) or 1-naphthaldehyde (4-11) and (*S*)-(–)-1-phenylethan-1-amine (4-29)

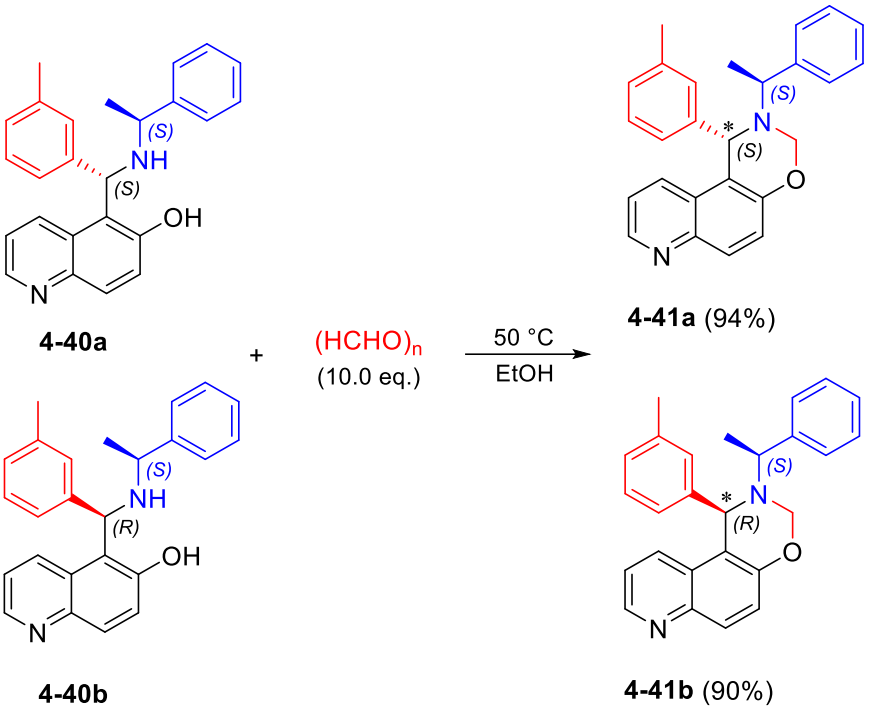
The condensation of quinolin-6-ol (**4-35**) with 3-methylbenzaldehyde (**4-19**) or 1-naphthaldehyde (**4-11**) and (*S*)-(–)-1-phenylethan-1-amine (**4-29**) proceeds upon heating at 80 °C in the absence of solvent (Scheme **C**). After column chromatography, the corresponding products were isolated as a mixture of two diastereoisomers in low yields. The ratio of **4-40a** to **4-40b** was 83:17, and that of **4-43a** to **4-43b** was 85:15, determined by $^1$H NMR spectroscopy. The predominant isomer **4-40a** was isolated in 19% yield after further recrystallization from diethyl ether/hexane, and **4-40b** was isolated in pure form after chromatographic purification of a pool of repeated experiments. The major diastereoisomer **4-43a** was isolated in 19% yield. The yield of diastereoisomer **4-43b** was determined by $^1$H NMR spectrum of the mixture (7% calculated yield).




**Scheme C** *Betti* Condensation of Quinolin-6-ol (**4-35**), 3-Methylbenzaldehyde (**4-19**) or 1-naphthaldehyde (**4-11**) and (*S*)-(−)-1-phenylethan-1-amine (**4-29**) (Scheme summarized in Table **4-5** and Scheme **4-28**)

The preparation of dihydro-1,3-oxazinquinolines from aminobenzylquinolinols has several important aspects. On the one hand, their reduction can yield *N*-substituted aminobenzylquinolinols, which can be used in asymmetric catalysis. On the other hand, compounds with an analogous structure exhibit pronounced biological activity. Dihydro-1,3-oxazinoquinolines have also been successfully used to determine the configuration of the newly formed stereogenic center (starred in Scheme **4-26**) using NMR experiments. The introduction of a methylene bridge between the N- and O-atom is a convenient synthetic method that does not affect the existing stereogenic centers, while reducing the conformational mobility of the molecule.

The isolated pure **4-40a** and **4-40b** were transformed into dihydro-1,3-oxazinquinolines **4-41a** and **4-41b** with paraformaldehyde on heating at 50 °C in ethanol (Scheme **4-26**). Products **4-41a** and **4-41b** were isolated in pure form in high yields of 94% and 90%, respectively.




**Scheme 4-26** Preparation of the dihydro-1,3-oxazinquinolines **4-41a** and **4-41b**

Attempts to reduce the dihydro-1,3-oxazinquinoline **4-41a** with $LiAlH_4$ were unsuccessful.

The synthesized aminobenzylquinolinols **4-40a**, **4-40b** and **4-43a** and dihydro-1,3-oxazinquinolines **4-41a** and **4-41b** were characterized using modern NMR techniques ($^1H$, $^{13}C$, *DEPT*, *COSY*, *HSQC*, *HMBC*, *NOESY*). This allows the signals for all protons and carbon atoms to be fully attributed.

One of the tasks of the dissertation is, by using appropriate NMR experiments and in the presence of a stereogenic center with a known absolute configuration, to determine the configuration of the newly formed stereogenic center in the synthesized aminobenzylquinolinols obtained by *Betti* condensation, and also in the corresponding dihydro-1,3-oxazinquinolines. From the *NOESY* experiments performed, it is possible to determine the protons characterized by spatial proximity to each other (Figure **4-7**). Based on this information, and with a known "*S*" configuration of the amine involved in the condensation, which does not change during the course of the reaction, meaning that it is also inherited in compounds **4-40a** and **4-41a**, one can with high probability determined the relative configuration of the newly formed C-11 stereogenic center as "*S*", after applying the *Cahn-Ingold-Prelog* rule for the seniority of substituents.

In the case of dihydro-1,3-oxazinquinoline **4-41a**, obtained after transformation of aminobenzylquinolinol **4-40a**, the newly formed stereogenic center C-11 turns out to be included in

a 6-membered ring, which is characterized by conformational stability. This provides an additional opportunity to determine with a greater degree of certainty the spatial arrangement of the substituents in the molecule by means of *NOESY* experiments (Figure **4-7**). Considering the known absolute configuration of the stereogenic center at C-13, which is "*S*", it can be concluded that the configuration of the newly formed stereogenic center at C-11 is also "*S*".

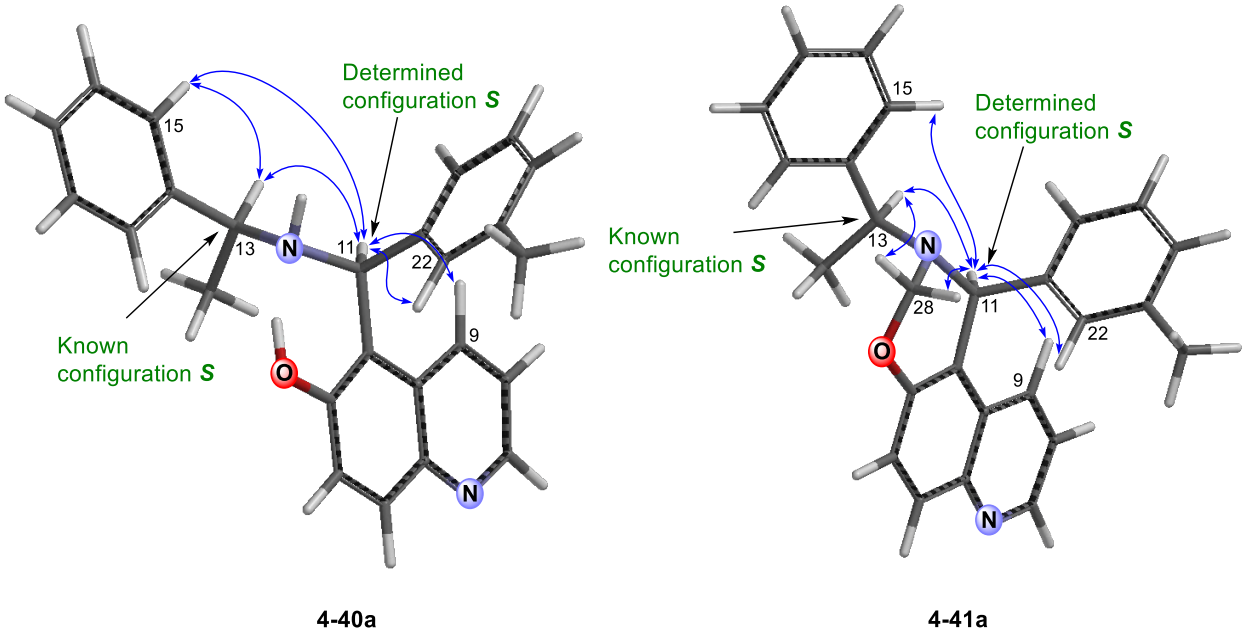



**Figure 4-7** Spatially close protons in the structures of **4-40a** and the corresponding dihydro-1,3-oxazinquinoline **4-41a**

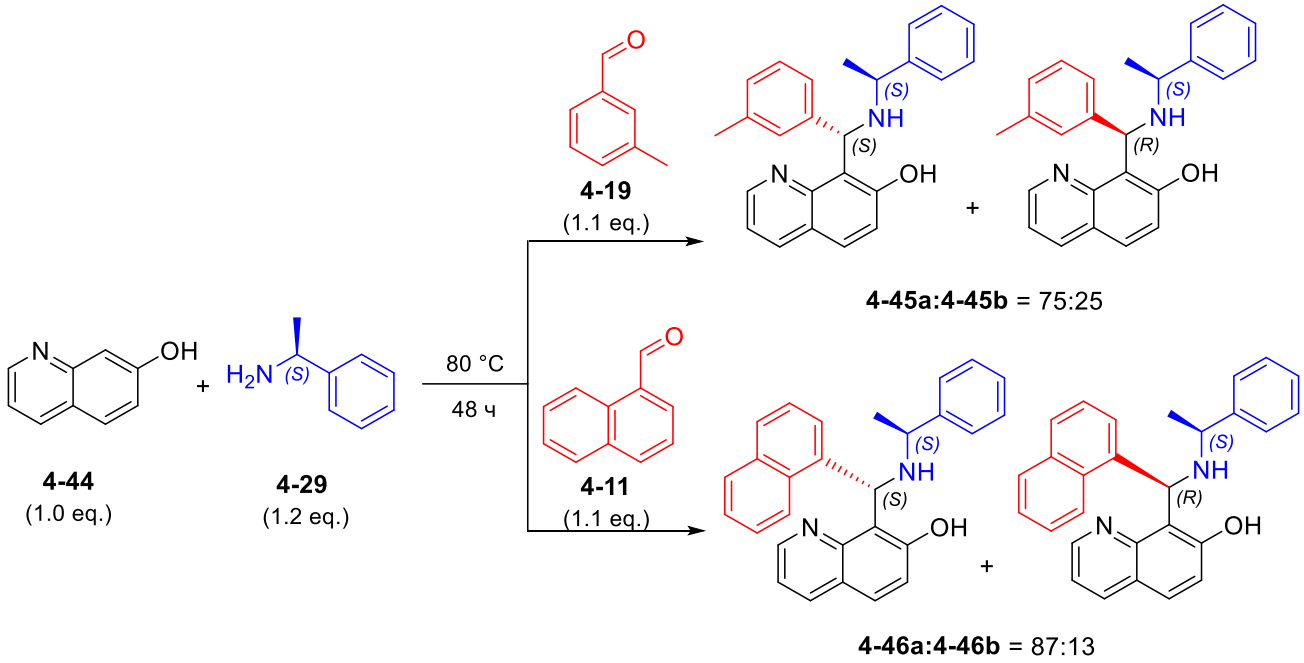
By means of X-ray structural analysis of a single crystal of the diastereomerically pure aminobenzylquinolinol **4-40a**, with a known absolute configuration at C-13, which is the "*S*" of the amine component, the absolute configuration of the newly formed C-11 stereogenic center was determined as "*S*", which coincides with that determined by NMR experiments.

### 4.6.4. *Betti* condensation of quinolin-7-ol (4-44) with 3-methylbenzaldehyde (4-19) or 1-naphthaldehyde (4-11) and (*S*)-(–)-1-phenylethan-1-amine (4-29)

In order to obtain new aminoquinolinols and study their catalytic activity, the condensation was carried out with another electron-rich component containing a heteroatom in its molecule, such as quinolin-7-ol (**4-44**).

The condensation of quinolin-7-ol (**4-44**) with 3-methylbenzaldehyde (**4-19**) or 1-naphthaldehyde (**4-11**) and (S)-(–)-1-phenylethan-1-amine (**4-29**) was carried out at 80 °C in the

absence of solvent for 48 h (Scheme **D**). After chromatographic purification, a mixture of two diastereoisomers **4-45a** and **4-45b** in a ratio of 75:25 and a mixture of two diastereoisomers **4-46a** and **4-46b** in a ratio of 87:13 were isolated, determined by $^{1}$H NMR spectroscopy. The predominant isomer **4-45a** was isolated in pure form with a yield of 28%, and **4-45b** with a yield of 6%. The diastereoisomeric mixture **4-46a** and **4-46b** could not be separated.




**Scheme D** *Betti* condensation of quinolin-7-ol (**4-44**), 3-methylbenzaldehyde (**4-19**) or 1-naphthaldehyde (**4-11**) and (*S*)-(−)-1-phenylethan-1-amine (**4-29**)
(summarized Scheme **4-29** and Scheme **4-30**)

In conclusion, it can be concluded that when using quinolin-6-ol or quinolin-7-ol, the condensation proceeds in low yields, despite conducting the reaction under different conditions, such as reaction time, the use of a solvent or not, and the use of additives. In all cases, the presence of unreacted starting components was found, as well as the corresponding imine obtained as a result of the reaction between aldehyde and amine.

Catalytic activity of **4-40a**, **4-40b**, **4-43a** and **4-45a** was investigated in addition reactions of $Et_2Zn$ to aldehydes. The degree of asymmetric induction is determined (Section **4.8.**).

## 4.7. A stereoselective strategy for the functionalization of 2,5-diketo-piperazine derived from L-proline and glycine

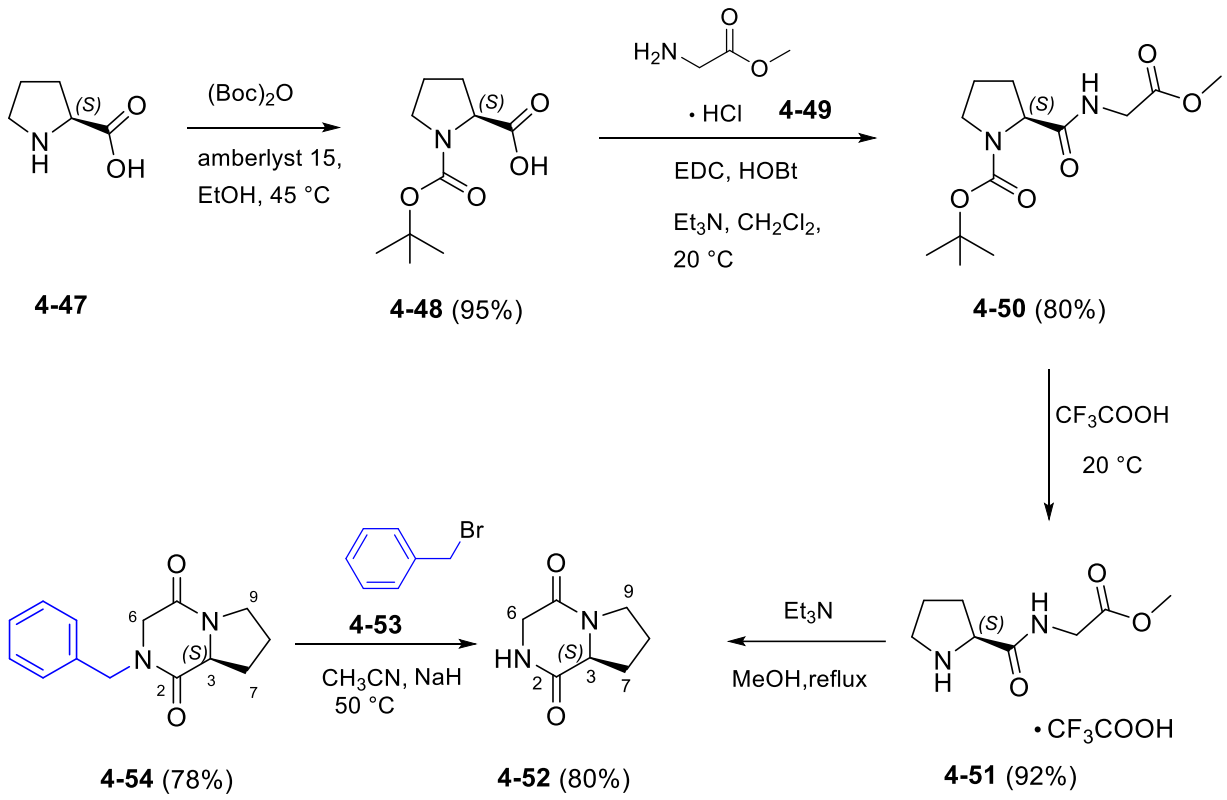
To achieve one of the goals of the dissertation, namely to obtain new chiral, enantiomerically pure compounds, a stereoselective strategy for the preparation of differently substituted 2,5-diketopipiperazines using the natural amino acid L-proline is proposed. Within the framework of the plan, we focused on the preparation of DCP from L-proline and glycine due to the possibilities of carrying out versatile subsequent functionalization reactions. The described experiments can be considered as a "proof of concept", providing, if successful, opportunities to develop and synthesize a series of new compounds with potential applicability.

### 4.7.1. Synthesis of diketopiperazine from L-proline and glycine and preparation of *N*-benzylated diketopiperazine

The synthesis of 2,5-diketopiperazine **4-52** was accomplished by cyclization of L-proline (**4-47**) and glycine methyl ester (**4-49**) in hydrochloride form using a literature procedure. The preparation of DCP was realized within 4 steps, without intermediate isolation of the products, with a total yield of 56% compared to the starting L-proline (Scheme **E**).

The overall yield of 56% is significantly higher than the reported literature yield of 38%.

*N*-Benzylation of **4-52** with benzyl bromide (**4-53**) was carried out using NaH in acetonitrile (Scheme **E**), and the product **4-54** was isolated in 78% yield. The overall yield of **4-54** relative to L-proline **4-47** was 44%.

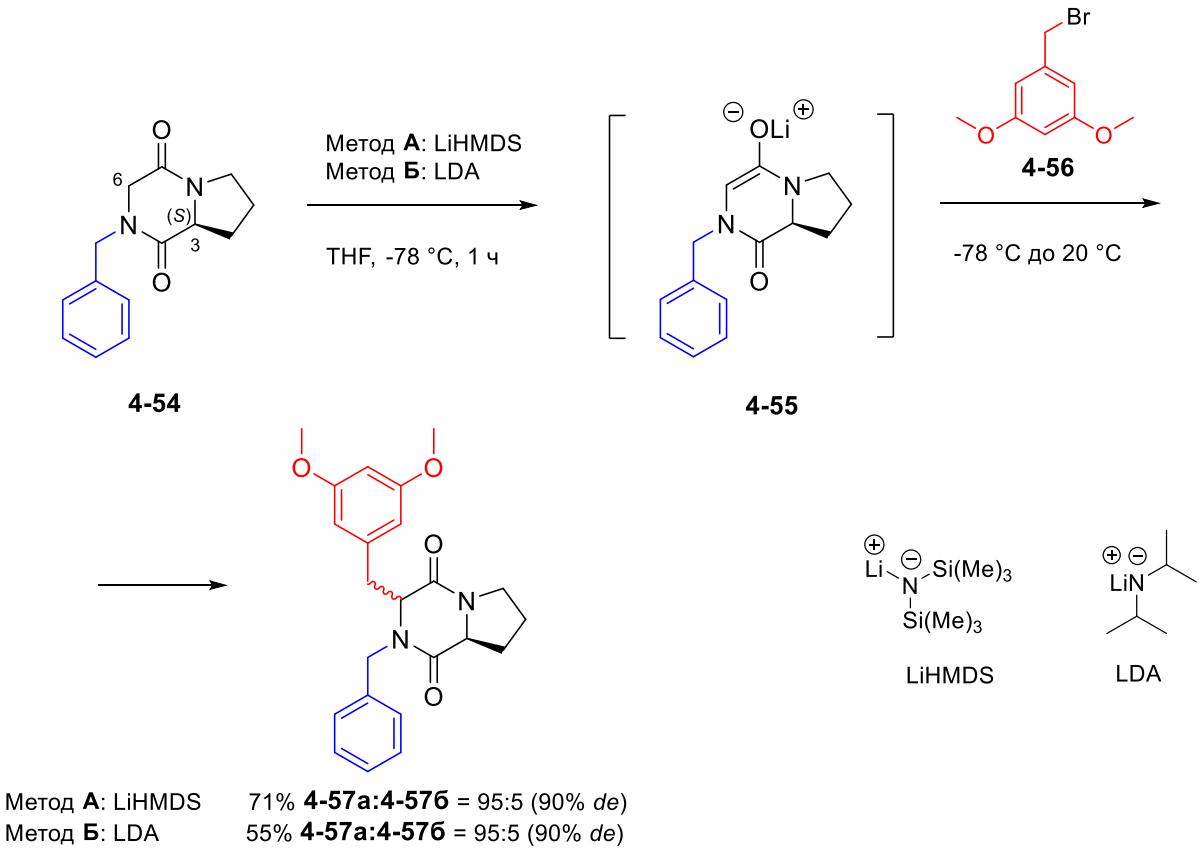



**Scheme E** Synthesis of **4-52** (Cyclo(Gly-Pro)) and subsequent *N*-benzylation to **4-54** (Scheme **4-31** and Scheme **4-32** summarized)

Only one example of the preparation of **4-54** in 56% yield by a multicomponent *Ugi* reaction has been reported in the literature. It is not considered that a 5-step scheme is required for the preparation of one of the starting compounds (2-(2-isocyanophenyl)acetaldehyde dimethyl acetal). Thus, the apparently one-step synthesis of **4-54** is complicated by the need to synthesize one of the starting substances, and in the end, the total yield of **4-54**, relative to the initial input of L-proline, is significantly reduced.

### 4.7.2. Alkylation of diketopiperazine 4-54 using 3,5-dimethoxy benzyl bromide (4-56)

For the introduction of various substituents in the 6th position of DKP **4-54**, it is necessary to first carry out deprotonation in the 6th position with subsequent alkylation with suitable electrophiles. Strong bases such as LiHMDS (lithium hexamethyldisilazide) or LDA (lithium diisopropylamide) can be used for deprotonation. Alkylation of the generated enolate **4-55** was carried out with 3,5-dimethoxybenzyl bromide (**4-56**) as a model compound (Scheme **4-33**).




**Scheme 4-33** Alkylation of 4-54 with 3,5-dimethoxybenzyl bromide (**4-56**) using LiHMDS (Method **A**) or LDA (Method **B**) as deprotonating agents

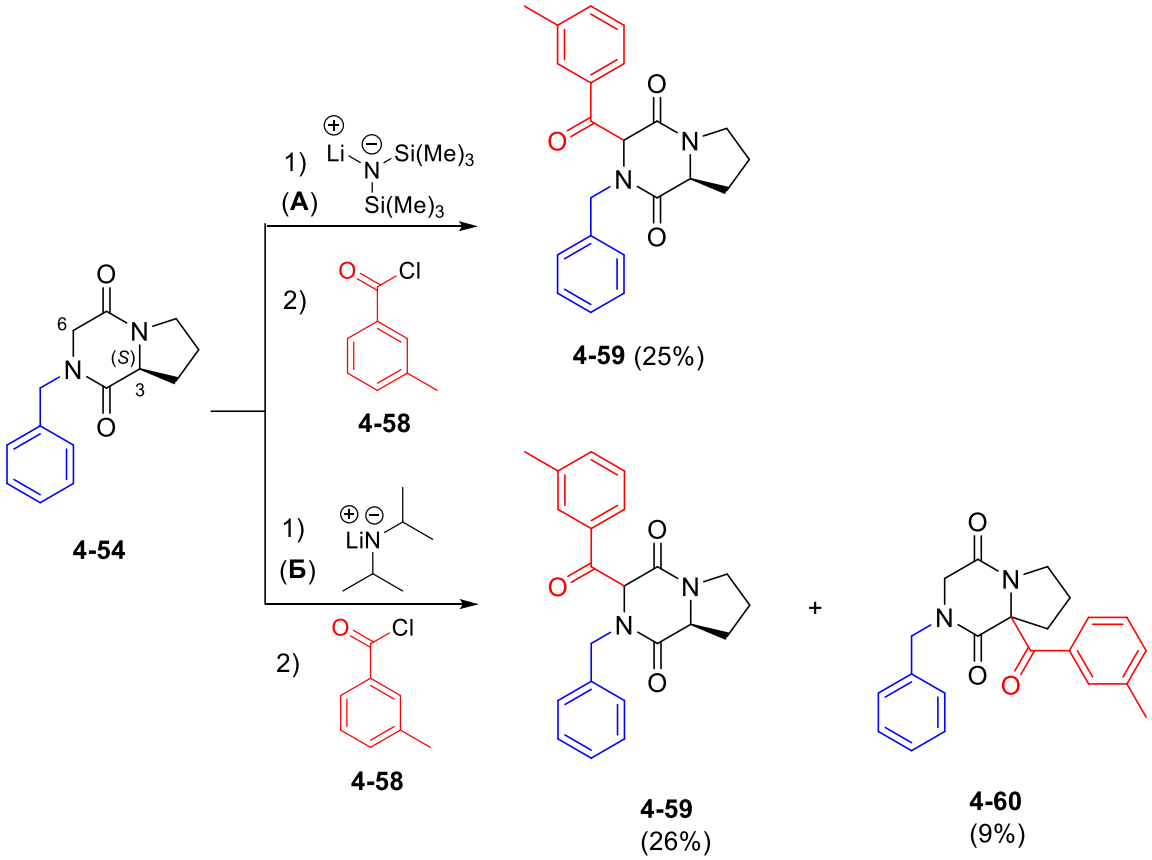
The product **4-57** was isolated in 71% yield (Method **A**) or 55% yield (Method **B**), as a mixture of two diastereoisomers (**4-57a**:**4-57b**) in a ratio in both cases of 95:5 (90% *de*) determined from NMR data. The two diastereoisomers have the same *Rf*-value and cannot be isolated in pure form separately from each other.

### 4.7.3. Acylation of diketopiperazine 4-54 using 3-methylbenzoyl chloride acid chloride (4-58)

Acylation reaction of **4-54** after deprotonation with LiHMDS or LDA with 3-methylbenzoyl chloride (**4-58**) (Scheme **4-34**) was carried out in order to obtain a variety of new products with DKP backbone.

Regardless of the deprotonating agent (LiHMDS or LDA), the expected product **4-59** was isolated after chromatographic purification in low yield (25% by method **A** and 26% by method **B**). Using LDA, 2 products (**4-59** and **4-60**) were isolated, resulting from acylation at the 6-position and at the 3-position of the DKP ring, respectively. Compounds **4-59** and **4-60** were isolated in pure form.

The by-product **4-60** was isolated in 9% yield. Using LiHMDS, only the 6-position acylation product was isolated (**4-59**). In both cases (method **A** or method **B**), only one diastereoisomer of **4-59** was isolated.




**Scheme 4-34** Acylation of **4-54** with 3-methylbenzoyl chloride (**4-58**) using LiHMDS (Method **A**) or LDA (Method **B**) as deprotonating agents

The experiments described in sections **4.7.1.** and **4.7.2.** demonstrate a successful synthesis based on literature data, in which DKP **4-54** is obtained efficiently and in good yields as a starting structure for synthetic stereoselective transformations. The optimized method of deprotonation and subsequent reaction with a suitable electrophile can be applied to the synthesis of a variety of multifunctional compounds. The results achieved in the so-called "proof of concept" provide good prospects for further developments beyond the scope of this thesis.

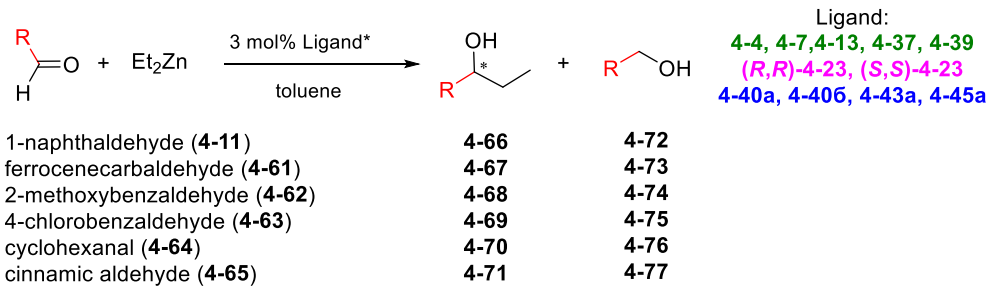
## 4.8. Application of newly synthesized chiral aminoalcohols as catalysts in enantioselective addition of diethylzinc to aldehydes

One of the goals of the dissertation is to study the catalytic properties of the newly obtained chiral amino alcohols **4-4**, **4-7**, **4-13**, **4-37**, **4-39**, (*R*,*R*)-**4-23**, (*S*,*S*)-**4-23**, **4-40a**, **4-40b**, **4-43a** and **4-46a** in the enantioselective addition of diethylzinc to aldehydes, due to their suitable structure and properties.

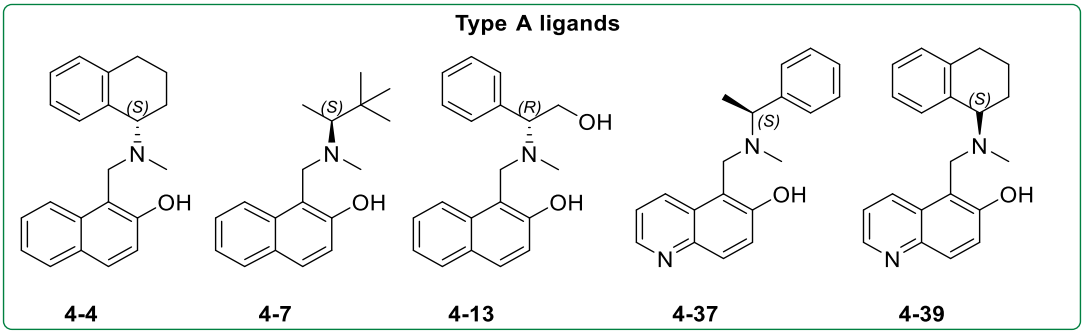
The addition reactions were carried out in an inert atmosphere, by a standard procedure applied and described many times in the specialized literature: The enantiomeric excess (*ee*) of the secondary alcohol obtained was determined by high-performance liquid or gas chromatography with chiral columns. The configuration of the obtained alcohols was determined by comparing the results with those obtained in analogous studies (retention time chromatographic and specific rotation angle).

For the purposes of the study, the ligands are divided into three groups, according to the type of substituents at the N-atom. The summarized results are systematized in Table **4-6**.

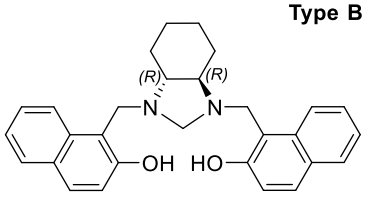
**Table 4-6** Catalytic activity of the synthesized ligands in the enantioselective addition of diethylzinc to aldehydes



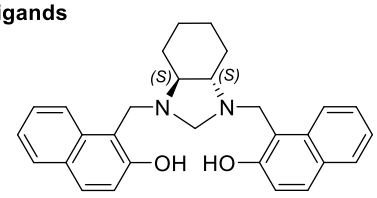

| | | |
|---|---|---|
| 1-naphthaldehyde (**4-11**) | **4-66** | **4-72** |
| ferrocenecarbaldehyde (**4-61**) | **4-67** | **4-73** |
| 2-methoxybenzaldehyde (**4-62**) | **4-68** | **4-74** |
| 4-chlorobenzaldehyde (**4-63**) | **4-69** | **4-75** |
| cyclohexanal (**4-64**) | **4-70** | **4-76** |
| cinnamic aldehyde (**4-65**) | **4-71** | **4-77** |



**Type B ligands**

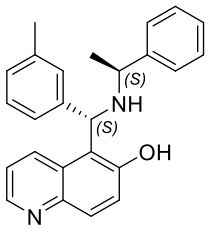


(*R*,*R*)-**4-23**

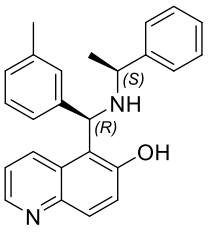


(*S*,*S*)-**4-23**

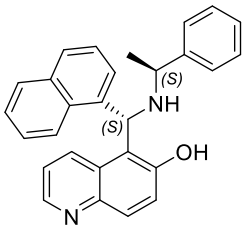
**Type C ligands**



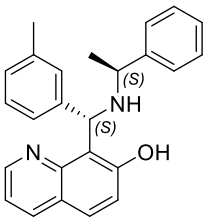
**4-40а**



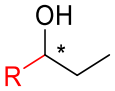
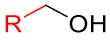
**4-40б**



**4-43а**



**4-45а**

| № | Ligand | Aldehyde | Time (h) | Product (yield[a]) (%) | | *ee* (*config.*) (%) |
|---|---|---|---|---|---|---|
| | | | |  |  | |
| 1 | **4-4** | 2-methoxybenzaldehyde | 48 | **4-68** (69) | – | 15 (*R*)[b] |
| 2 | **4-4** | 1-naphthaldehyde | 48 | **4-66** (34) | **4-72** (20) | 0 |
| 3 | **4-7** | 2-methoxybenzaldehyde | 120 | **4-68** (56) | – | 6 (*R*)[b] |
| 4 | **4-7** | 1-naphthaldehyde | 120 | **4-66** (56) | – | 3 (*R*)[c] |
| 5 | **4-13** | 2-methoxybenzaldehyde | 72 | **4-68** (57) | – | 11 (*R*)[b] |
| 6 | **4-37** | 2-methoxybenzaldehyde | 48 | **4-68** (74) | – | **39 (*R*)**[b] |
| 7 | **4-37** | 1-naphthaldehyde | 123 | **4-66** (36) | **4-72** (57) | 3 (*R*)[c] |
| 8 | **4-39** | 2-methoxybenzaldehyde | 48 | **4-68** (88) | – | 24 (*R*)[b] |
| 9 | **4-39** | 1-naphthaldehyde | 72 | **4-66** (54) | **4-72** (24) | 0 |
| 10 | (*R*,*R*)-**4-23** | 2-methoxybenzaldehyde | 72 | **4-68** (66) | – | **53 (*R*)**[b] |
| 11 | (*S*,*S*)-**4-23** | 2-methoxybenzaldehyde | 24 | **4-68** (80) | – | **58 (*S*)**[b] |
| 12 | (*R*,*R*)-**4-23** | 1-naphthaldehyde | 52 | **4-66** (45) | **4-72** (30) | 39 (*R*)[c] |
| 13 | (*S*,*S*)-**4-23** | 1-naphthaldehyde | 120 | **4-66** (54) | – | 30 (*S*)[c] |
| 14 | (*R*,*R*)-**4-23** | 4-chlorobenzaldehyde | 144 | **4-69** (90) | – | 49 (*R*)[c] |
| 15 | (*S*,*S*)-**4-23** | 4-chlorobenzaldehyde | 120 | **4-69** (30) | – | 50 (*S*)[c] |
| 16 | (*R*,*R*)-**4-23** | cyclohexanal | 24 | **4-70** (46) | – | 38 (*S*)[b] |
| 17 | (*S*,*S*)-**4-23** | cyclohexanal | 24 | **4-70** (49) | – | 40 (*R*)[b] |
| 18 | (*R*,*R*)-**4-23** | ferrocenecarbaldehyde | 48 | **4-67** (80) | – | 38 (*R*)[c] |

| | | | | | | |
|---|---|---|---|---|---|---|
| 19 | (*S*,*S*)-**4-23** | ferrocenecarbaldehyde | 120 | **4-67** (74) | – | 42 (*S*)[c] |
| 20 | **4-40а** | 2-methoxybenzaldehyde | 24 | **4-68** (84) | – | **93 (*R*)[b]** |
| 21 | **4-40б** | 2-methoxybenzaldehyde | 48 | **4-68** (68) | – | 63 (*S*)[b] |
| 22 | **4-40а** | 1-naphthaldehyde | 120 | **4-66** (66) | **4-72** (24) | 10 (*R*)[c] |
| 23 | **4-40б** | 1-naphthaldehyde | 48 | **4-66** (14) | **4-72** (22) | 18 (*S*)[c] |
| 24 | **4-40а** | 4-chlorobenzaldehyde | 168 | **4-69** (61) | **4-75** (14) | 23 (*R*)[c] |
| 25 | **4-40б** | 4-chlorobenzaldehyde | 168 | **4-69** (56) | – | 16 (*S*)[c] |
| 26 | **4-40а** | cyclohexanal | 24 | **4-70** (29) | – | 14 (*S*)[b] |
| 27 | **4-40а** | ferrocenecarbaldehyde | 24 | **4-67** (89) | – | **96 (*R*)[c]** |
| 28 | **4-40а** | cinnamic aldehyde | 48 | **4-71** (53) | – | 72 (*R*)[c] |
| 29 | **4-43а** | 2-methoxybenzaldehyde | 24 | **4-68** (62) | – | **95 (*R*)[b]** |
| 30 | **4-43а** | 1-naphthaldehyde | 48 | **4-66** (31) | **4-72** (35) | 40 (*R*)[c] |
| 31 | **4-43а** | 4-chlorobenzaldehyde | 114 | **4-69** (62) | – | 53 (*R*)[c] |
| 32 | **4-43а** | cyclohexanal | 24 | **4-70** (41) | – | 50 (*S*)[b] |
| 33 | **4-43а** | ferrocenecarbaldehyde | 24 | **4-67** (89) | – | **98 (*R*)[c]** |
| 34 | **4-43а** | cinnamic aldehyde | 48 | **4-71** (77) | – | 75 (*R*)[c] |
| 35 | **4-45а** | 2-methoxybenzaldehyde | 48 | **4-68** (76) | – | 86 (*R*)[c] |
| 36 | **4-45а** | cyclohexanal | 48 | **4-70** (67) | – | 12 (*S*)[b] |
| 37 | **4-45а** | ferrocenecarbaldehyde | | **4-67** (93) | – | 96 (*R*)[c] |

[a]The yield is of products isolated in pure form after column chromatography
[b]Enantiomeric excess was determined by GC analyses
[c]Enantiomeric excess was determined by HPLC analyses.

From the reactions performed for the enantioselective addition of diethylzinc to aldehydes catalyzed by the three groups of chiral non-racemic ligands listed above, the following conclusion can be drawn: Ligands of type **A** obtained by *Mannich* condensation of naphthalene-2-ol, formaldehyde and chiral amines, exhibit low enantioselectivity, which is most likely due to the mobility of the methylene bridge between the nitrogen atom of the amine component and the carbon atom of the naphthol or quinolinol component, respectively. In the second group of **B**-type ligands with an imidazolidine ring in the molecule, a moderate asymmetric induction was recorded, despite the presence of two zinc atom coordination centers. With the third group of **C**-type ligands, which are representatives of the so-called "*Betti* bases", in which the naphthol component is replaced by a quinolinol component, a very high enantioselectivity of up to 98% *ee* was registered, as expected.

## 4.9. Biological activity

### 4.9.1. Evaluation of antimicrobial activity

To evaluate the antimicrobial activity of compounds **4-12**, **4-36**, **4-37**, **4-40a**, **4-41a** and **4-45a** (Fig. **4-10**) were used 3 bacterial test pathogens (gram-positive and gram- negative): *Bacillus cereus* ATCC 11778, *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 25923 and yeast strain *Candida albicans* ATCC 10231.

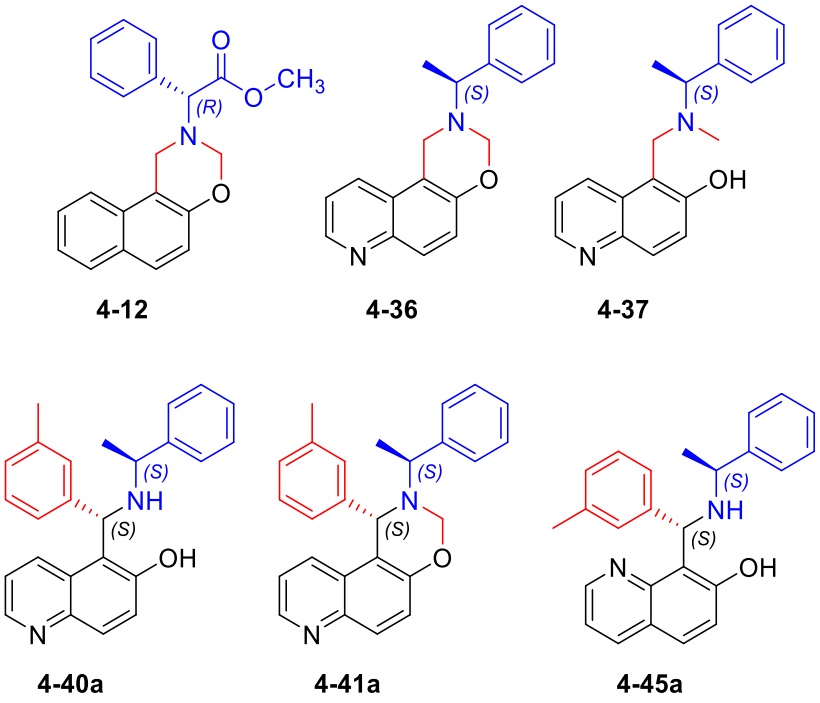



**Figure 4-10** Structure of synthesized compounds **4-12**, **4-36**, **4-37**, **4-40a**, **4-41a** and **4-45a** tested for antimicrobial activity

For the correct implementation of the experiments, antibiotic discs suitable for each relevant test pathogen were used as positive controls. The (+) control used for the bacterial test pathogen was *Gentamicin* and for the yeast strain (+) control was *Nystatin*.

The results of the antimicrobial activity evaluation of the tested samples are presented graphically in Figure **4-11**, showing the zones of inhibition. The inhibition effect of the samples was also evaluated as % of (+) control (Figure **4-12**).

Based on the data presented and the results obtained, it can be seen that only two of the investigated synthetic substances, namely (**4-37** and **4-41a**), analogues of BAS, exhibit biological activity towards various test pathogens (Figure **4-11**). The synthetic substance **4-41a** was found to

have antimicrobial activity against the test pathogen *Bacillus cereus* when it was applied at a higher concentration – 0.1 mg/ml. When applying the compound in a lower concentration – 0.05 mg/ml, no such effect is observed. In **4-37**, antibacterial activity was found at the two tested concentrations - 0.14 mg/ml and 0.07 mg/ml against the test culture *Staphylococcus aureus*. The inhibition effect of the two biologically active substances was determined, and for **4-41a** it was 42% of that of the (+) control, and for **4-37** it was 50 to 52% of that of the (+) control at the two analyzed concentrations (Figure **4-12**).

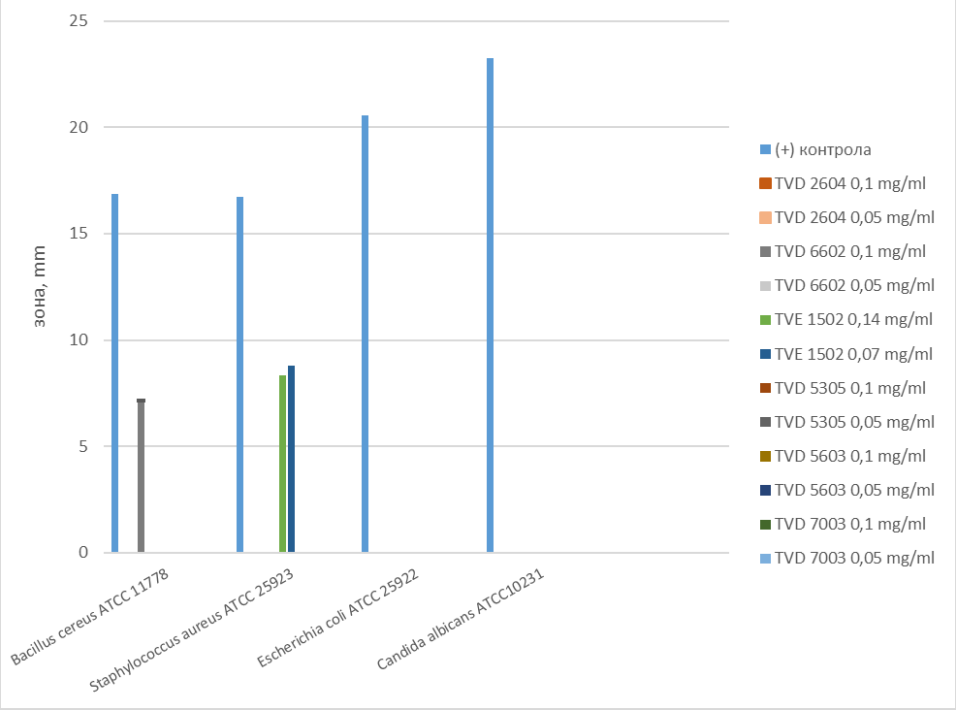



**Figure 4-11** Results of the evaluation of antimicrobial activity as reported zones of inhibition of the tested samples, analogs of synthetic substances of BAS

Regarding the other tested substances, no antimicrobial activity was found against the tested bacterial pathogens and yeast strain, which may be due to the difficulties in dissolving the samples and, accordingly, in the subsequent diffusion of the tested substances in the agar media.

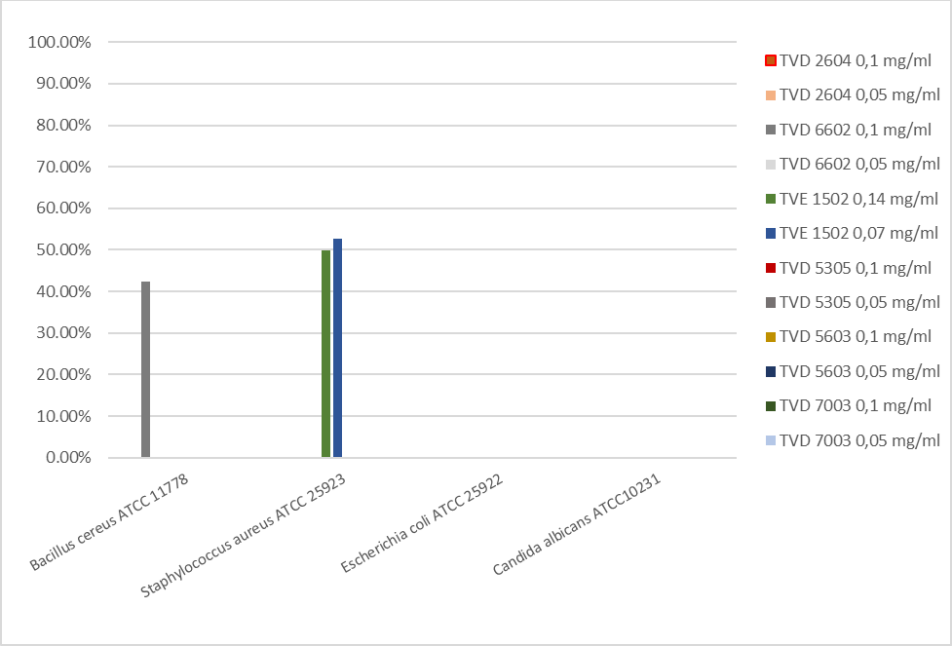



**Figure 4-12** Inhibition effect in the tested samples of synthetic analogues of BAS, as % of (+) control of the tested samples

### 4.9.2. Evaluation of antiviral activity

Compounds **4-12**, **4-40a** and **4-41a** depicted in Figure **4-10** were tested for antiviral activity. the MNC (Maximum Non-Toxic Concentration relative to the cell line) was determined (Table **4-7**).

**Table 4-7** Activity of solutes **4-12**, **4-40a**, and **4-41a** against cell culture (MDBK) and viral replication (HSV-1)

| Substance | MNC μg/ml | $CTC_{50}$ μg/ml | $IC_{50}$ μg/ml |
|---|---|---|---|
| **4-40a** | 15 | 25.03 | - |
| **4-41a** | 15 | 18.23 | - |
| **4-12** | 100 | - | 93.8 |

The determination of the 50% cytotoxic concentration ($CTC_{50}$) is based on a spectrophotometric study.

Based on the viability test, dose-dependent curves were constructed (Fig. **4-13**), as the cells were exposed to solutions of the investigated substances with increasing concentration. The constructed curves allowed the determination of $CTC_{50}$ for substances **4-40a**, **4-41a** and **4-12**. The determination of $CTC_{50}$ is done graphically using the constructed "dose (concentration)-cell survival" curve.

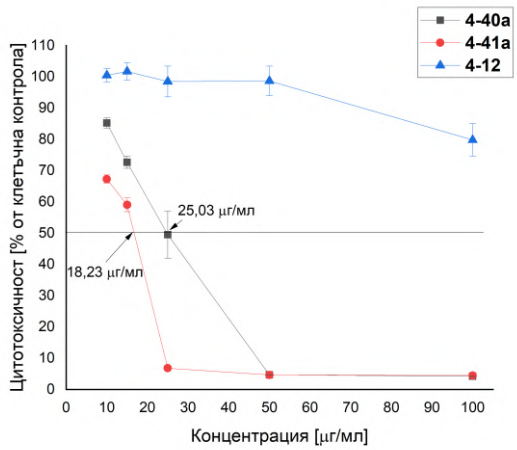



**Fig. 4-13** Dose-dependent cytotoxicity curves against MDBK cell culture

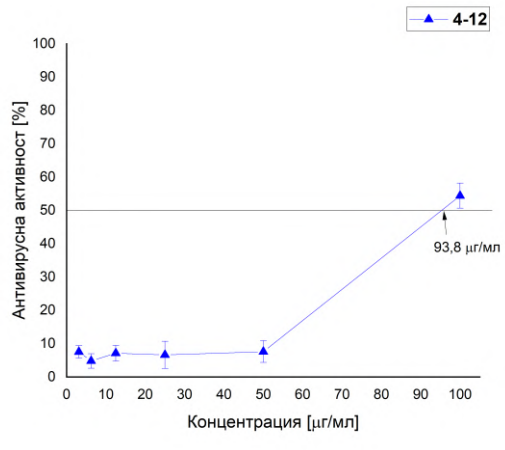


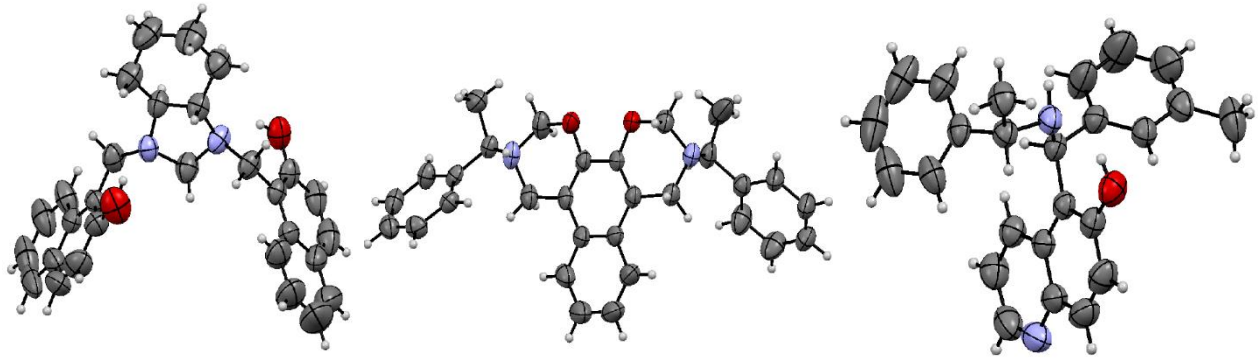

**Fig. 4-14** Antiviral activity of substance **4-12** against HSV-1 strain F

After determining the effect on the MDBK cell line used, the test substances were tested for antiviral activity against HSV-1 (herpes simplex virus type 1, strain F) ((*Simplex virus humanalpha1*) (https://ictv.global)). Regarding its replication, only substance **4-12** showed antiviral activity, and only in MNK it reached 58.7% inhibition of viral replication. On the basis of the constructed dose-dependent curve, this also allows determination of a 50% inhibitory concentration – 93.8µg/ml (Fig. **4-14**).

The values observed for both the cell line and the virus suggest a lower activity than the gold standard in herpesvirus therapy, Acyclovir and its derivatives.

## Structural information

The structure of compounds (*R*,*R*)-**4-23**, **4-30** and **4-40a** was unambiguously confirmed by single crystal X-ray diffraction analysis.



(*R*,*R*)-**4-23** **4-30** **4-40a**

ORTEP view of compounds (*R*,*R*)-**4-23**, **4-30** and **4-40a**, H atoms are represented by spheres of arbitrary radii and ellipsoids are at 50% probability

# 5. CONCLUSIONS

1. Dihydro-1,3-naphthoxazines were synthesized by *Mannich* condensation of naphthalen-2-ol, formaldehyde and various chiral amines. The compounds are intermediates for the synthesis of tertiary *N*-substituted amino alcohols obtained after reduction.
2. Natural amino acid derivatives – (*R*)-(–)-2-phenylglycinol and methyl ester of (*R*)-(–)-2-phenylglycine were used as a source of chirality in *Mannich* condensation with formaldehyde and naphthalene-2-ol in order to obtain a chiral aminodiol. It was proved that in both cases the reaction proceeds with preservation of the configuration of the starting chiral components.
3. Bis-dihydro-1,3-naphthoxazines were synthesized in high yield by three-component *Mannich* condensation of 2,3- or 2,6-dihydroxynaphthalenes with formaldehyde and (*S*)-(–)-1-phenylethan-1-amine.
4. A *Mannich* condensation of naphthalene-2-ol, formaldehyde and (*R*,*R*)- or (*S*,*S*)-cyclohexane-1,2-diamine was carried out. Optimal conditions for preferential formation of chiral, non-racemic imidazolidine bis-hydroxynaphthalene were found.
5. Three-component *Betti*-type condensation of quinoline analogues of naphthalen-2-ol (quinolin-6- or 7-ol) with aromatic aldehydes (3-methyl-benzaldehyde and 1-naphthaldehyde) and S-(–)-1-phenylethan-1-amine. The reactions proceed with high diastereoselectivity. In the case of quinolin-6-ol derivatives with 1-naphthaldehyde, only one of the two diastereoisomers was isolated, and when using 3-methylbenzaldehyde, it was possible to isolate both diastereoisomers in pure form. In the case of quinolin-7-ol derivatives with 1-naphthaldehyde, an inseparable mixture of the two diastereoisomers in a ratio of 87:13 was isolated, and when using 3-methylbenzaldehyde, it was possible to isolate both diastereoisomers in pure form.
6. The newly synthesized chiral compounds were fully characterized using NMR spectroscopy, mass spectrometry, specific rotation angle and elemental analysis.
7. The configuration of the newly formed stereogenic center of aminobenzylquinolinol **4-40a** was determined by means of modern NMR techniques. The applicability of the NMR approach for determining the configuration of this type of compounds has been proven by X-ray structural analysis.
8. The synthesized chiral nonracemic ligands (divided into 3 groups) were used as catalysts in the model reaction for the enantioselective addition of diethylzinc to aldehydes. Ligands obtained by *Mannich* condensation of naphthalene-2-ol, formaldehyde and chiral amines were found to exhibit low enantioselectivity. For ligands with an imidazolidine ring in the molecule, a

moderate asymmetric induction was recorded. High enantioselectivity – up to 98% *ee* – was achieved with the ligands obtained via *Betti* condensation from quinoline-6- or 7-ol, aldehydes and (*S*)-(−)-1-phenylethan-1-amine.

9. A novel substituted diketopiperazine was synthesized by implementing a synthetic strategy based on deprotonation with LiHMDS (method **A**) or LDA (method **B**) and subsequent alkylation with 3,5-dimethoxybenzyl bromide in 71% and 55% yields, respectively. The reaction is highly diastereoselective as determined by NMR spectroscopy (92% *de*). Two new substituted diketopiperazines were synthesized by deprotonation with LiHMDS (method **A**) or LDA (method **B**) and subsequent acylation with 3-methylbenzoyl chloride. In the first case, only one product acylated at position 6 is isolated. In the second case, 2 products are isolated as a result of acylation at position 3 and position 6.
10. The isolated intermediates and final products of the diketopiperazine Cyclo(Gly-Pro) derivatives were characterized using NMR spectroscopy, mass spectrometry, M.p. and elemental analysis. By using two-dimensional NMR techniques, a complete assignment of the protons and C-atoms of the newly obtained products was made.
11. The biological activity of selected compounds was evaluated as follows: For substance **4-41a**, antimicrobial activity against the test pathogen *Bacillus cereus* was found when it was applied in a higher concentration – 0.1 mg/ml. When applying the compound in a lower concentration – 0.05 mg/ml, no such effect is observed. In **4-37**, antibacterial activity was found at the two tested concentrations – 0.14 mg/ml and 0.07 mg/ml against the test culture *Staphylococcus aureus*. The inhibition effect of the two substances was also determined, with **4-41a** being 42% of that of the (+) control, and with **4-37** being 50 to 52% of that of the (+) control at the two analyzed concentrations. Only substance **4-12** showed antiviral activity, but only in MPC – just over 50% inhibition of viral replication.

## List of scientific activity on the topic of the dissertation of assistant Maya Tavlinova-Kirilova

### List of scientific publications and citations noted on the topic of the dissertation

1. **Tavlinova-Kirilova, M.**, Marinova, M., Angelova, P., Kamenova-Nacheva, M., Kostova, K., Dimitrov, V., *Bulgarian Chemical Communications*, **2016**, *48*, 4, 705-712. Three component condensation of Betti-type – efficient tool for synthesis of chiral naphthoxazines and aminobenzylnaphthols for enantioselective diethylzinc addition to aldehydes.

JCR category rank **Q4**

1. Slitikov, P. V., Evdokimenkova, Y. B., *Herald of the Bauman Moscow State Technical University, Series Natural Sciences*, **2021**, *1*(94), 126-143. Aminomethylated Hydroxinaphthalenes: Synthesis and Application.
2. Ganesh, S., Sarika, K., Reddy, P. N., Padmaja, P., *Current Catalysis*, **2021**, *10*(1), 75-80. Synthesis of New Chiral *N*-alkyl *Betti*-base Ligands via One-Pot Three Component Strategy.

2. Petrova, A., Pancheva, M., Kostova, K., Zagranyarska, I., **Tavlinova-Kirilova, M.**, Dimitrov, V., *Bulgarian Chemical Communications*, **2017**, *49*, Special Issue B, 18-24. Stereoselective functionalization strategy of 2,5-diketopiperazine derived from L-proline and glycine.

JCR category rank **Q4**

3. **Tavlinova-Kirilova, M.**, Dikova, K., Marinova, M. K., Kamenova-Nacheva, M., Rusew, R., Sbirkova-Dimitrova, H., ... & Dimitrov, V., *Crystals*, **2023**, *13*(10), 1495. Synthesis and Structural Analysis of Chiral Bis-dihydro [1,3]-naphthoxazines and Imidazolidine Derivatives Prepared by Three-Component *Mannich*-Type Condensation.

JCR category rank **Q2**

## List of scientific conference participations on the topic of the dissertation

1. 21st International Conference on Organometallic Chemistry;
   Bratislava, Slovakia; 05.07.2015 – 09.07.2015 г.
   Kostova, K., Tavlinova-Kirilova, M., Marinova, M., Zagranyarska, I., Dikova, K., Dimitrov, V. *Diastereoselective synthesis of chiral aminonaphthols for enantioselective addition of diethylzinc to aldehydes* (Poster).

2. 25th Congress of the Society of Chemists and Technologists of Macedonia;
   Ohrid, Macedonia; 19.09.2018 – 22.09.2018 г.
   Tavlinova-Kirilova, M., Kostova, K., Kamenova-Nacheva, M., Nikolova, R., Shivachev, B., Dimitrov, V. *Mannich-Type Approach to Chiral Amino-Quinolinols - Synthesis and Application* (Poster)

3. VIIth National Crystallographic Symposium with International Participation
   Sofia, Bulgaria; 03.10.2018 – 05.10.2018 г.
   Dikova, K., Tavlinova-Kirilova, M., Kostova, K., Chimov, A., Nikolova, R., Shivachev, B., Dimitrov, V. *Synthesis of chiral aminoalcohols-configuration determination and catalytic application* (Poster)

4. Scientific Conference: Research Infrastructure in support of Science, Technology and Culture
   Sofia, Bulgaria; 29.09.2020 – 30.09.2020 г.
   Tavlinova-Kirilova, M., Kamenova-Nacheva, M., Kostova, K., Dimitrov, V. *Synthesis of Chiral, non-Racemic Aminonaphthols and Determination of their Chiroptical Properties Using a Polarimeter* (Poster)

5. Scientific Conference: Research Infrastructure in support of Science, Technology and Culture
   Sofia, Bulgaria; 29.09.2020 – 30.09.2020 г.
   Kamenova-Nacheva, M., Tavlinova-Kirilova, M., Kostova, K., Dimitrov, V. *Enantioselective Addition of $Et_2Zn$ to Aldehydes - Determination of Enantiomeric Excess by High-Performance Liquid Chromatography (HPLC)* (Poster)

6. Scientific Conference: Research Infrastructure in support of Science, Technology and Culture
   Pravetz, Bulgaria; 08.09.2021 – 10.09.2021 г.
   Kamenova-Nacheva, M., Tavlinova-Kirilova, M., Kostova, K., Dimitrov, V. *Synthesis of chiral, non-racemic aminonaphthols and determination of their chiroptical properties using a polarimeter* (Poster)

7. Scientific Conference: Research Infrastructure in support of Science, Technology and Culture
   Plovdiv, Bulgaria; 12.09.2022 – 14.09.2022 г.
   Kamenova-Nacheva, M., Tavlinova-Kirilova, M., Kostova, K., Dimitrov, V. *Synthesis of bis-dihydro-1,3-naphthoxazines using 1,2-cyclohexanediamine or dihydroxynaphthalenes in Mannich condensation* (Poster)