Asymmetric Synthesis of C_2-Symmetric Bimorpholines and Their Application as Chiral Ligands in the Transfer Hydrogenation of Aromatic Ketones

KADRI KRIIS

TUT PRESS

TALLINN UNIVERSITY OF TECHNOLOGY

Department of Chemistry
Chair of Organic Chemistry

Dissertation in Organic Chemistry to be publicly examined
at Tallinn University of Technology, on January 20, 2004
for the Degree of Doctor of Philosophy

Supervisors: Professor Margus Lopp, Ph. D.
Associate Professor Tõnis Kanger, Ph. D.

Opponents: Professor Asko Uri, Ph. D., Institute of Organic and Bioorganic Chemistry,
University of Tartu, Estonia
Senior Research Scientist Lauri Vares, Ph. D., AstraZeneca AB, Sweden

ISSN 1406-4723
ISBN 9985-59-412-6

Abstract

The chiral heteroatom-containing compounds are valuable synthons in the asymmetric synthesis. The combination of C_2-symmetry and the rigidity of the heterocycles can be a determining factor for effectiveness in the asymmetric reactions. The chiral ligands in the conformationally restricted chelation with metal can increase the stereodifferentiation for various metal mediated reactions. They can cause an efficient chirality transfer from the heterocycle to the newly formed bonds, thereby generating new stereogenic centers with high asymmetric induction.

Based on these positive properties, in the first part of this thesis the synthesis of two new chiral *N*,*O*-containing bicycles - *2S,2´S*- and *3S,3´S*-bimorpholine has been studied. (*R*,*R*)-tartaric acid ester, as a very convenient precursor, was chosen for the synthesis of both target compounds. The general scheme for the synthesis of these C_2-symmetric bimorpholines consists of three major steps: introduction of the nitrogen-containing functionality into the tartaric acid derivative, *O*-alkylation of hydroxyl groups with a functionalised C2 unit, and subsequent intramolecular cyclisation. Tartaric acid derivative was converted into bimorpholines with retention or inversion of the configuration of its stereogenic centres. A suitable *O*-alkylating reagent for the construction of C_2-symmetric intermediates with appropriately elongated chains was found. A number of methods for intramolecular cyclisation to obtain heterocycles were studied and an appropriate way to realise it was found. The elaborated synthetic route is quite simple and allows preparing both enantiomers of 2,2´- and 3,3´-bimorpholine. The NMR analysis showed that the enantiomeric excess of both bimorpholines is very high (*ee* >98%).

Nitrogen-containing compounds have been successfully used for the asymmetric transfer hydrogenation of ketones, most commonly with rhodium and ruthenium metal-complexes. The use of different chiral catalysts based on the obtained bimorpholines in the asymmetric transfer hydrogenation of ketones is the major goal of the second part of this work.

3S,3´S-bimorpholine as 1,2-diamine was found to be a suitable ligand for metal mediated transfer hydrogenation. The reason why *2S,2´S*- bimorpholine as ligand failed to give the asymmetric induction could be the difference in the geometry of the metal-chelated complexes.

The highest catalytic activity in the reduction was obtained when the complex was derived from *3S,3´S*-bimorpholine and $[Rh(cod)Cl]_2$. The stereoselectivity of the catalytic system is strongly dependent on the structure of the substrate. Reduction of the ketones sterically more hindered afforded a higher enantioselectivity (up to 77%). The activity and stereoselectivity of the catalyst depends on several factors (such as the molar ratio of the catalyst components, temperature and the substrate concentration).

In this work has demonstrated that *3S,3´S*-bimorpholine is a promising ligand for metal mediated asymmetric reactions.

C_2-sümmeetriliste bimorfoliinide asümmeetriline süntees ja kasutamine kiraalse ligandina ketoonide hüdriid-ülekandega taandamisel

Kokkuvõte

Kiraalsed heteroaatomit sisaldavad ühendid on ühed hinnatuimad asümmeetrilises sünteesis. C_2-sümmeetria ja jäiga heterotsüklilise struktuuri kombinatsioon võib määrata ühendi efektiivsuse tema kasutamisel asümmeetrilistes reaktsioonides. Kiraalse ligandi komplekseerumisel metalliga moodustub konformatsiooniliselt jäik kelaat, mis võib suurendada mitmete metall-katalüütiliste reaktsioonide stereodifferentseeritust, põhjustades seega efektiivset kiraalsuse ülekannet ligandi heterotsüklilisest struktuurist uude moodustunud ühendisse ja andes kõrge asümmeetrilise induktsiooniga stereogeenseid tsentreid.

Neile positiivsetele omadustele põhinedes on antud töö esimeses osas esitatud kahe uue kiraalse *N*,*O*-sisaldava bitsüklilise ühendi - *2S,2´S*- ja *3S,3´S*-bimorfoliini süntees. Mõlemale bimorfoliinile on väga sobivaks lähteaineks (*R*,*R*)-viinhappe ester. C_2-sümmeetriliste bimorfoliinide sünteesi üldskeem sisaldab kolme põhietappi: lämmastik-funktsionaalsuse sisseviimine viinhappe derivaati, hüdroksüülrühmade *O*-alküleerimine ja sisemolekulaarne tsükliseerimine. Bimorfoliinide absoluutne konfiguratsioon on määratud viinhappe derivaadi stereogeensete tsentrite konfiguratsiooni säilimise või pöördumisega sünteesil. Leiti pikendatud ahelaga C_2-sümmeetriliste vaheühendite sünteesiks sobiv *O*-alküleeriv reagent. Rea sisemolekulaarse tsüklisatsiooni reaktsioonide uurimisel jõuti rahuldava meetodini. Väljatöötatud sünteesitee on suhteliselt lihtne ja võimaldab sünteesida 2,2´- ja 3,3´-bimorfoliini mõlemat enantiomeeri. Vastavalt TMR analüüsile on sünteesitud bimorfoliinid kõrge enantiomeerse puhtusega (*ee* >98%).

Lämmastikku sisaldavaid ühendeid on edukalt kasutatud ketoonide asümmeetrilisel hüdriid-ülekandega taandamisel, enamasti roodium- ja ruteenium-kompleksides. Käesoleva töö teises osas on esitatud bimorfoliinidest sünteesitud erinevate katalüütiliste komplekside kasutamine ketoonide asümmeetrilisel hüdriid-ülekandega taandamisel.

3S,3´S-bimorfoliin kui 1,2-diamiin osutus sobivaks ligandiks metall-katalüütilisele hüdriid-ülekandega taandamisele. *2S,2´S*-bimorfoliini mittesobivus võib olla seletatav erinevusega moodustunud metall-komplekside geomeetrias. *3S,3´S*-bimorfoliinist ja $[Rh(cod)Cl]_2$ valmistatud kompleks andis taandamisel parima katalüütilise aktiivsuse. Katalüütilise süsteemi stereoselektiivsus on tugevalt mõjutatud substraadi struktuurist. Steeriliselt enamtakistatud ketoonide taandamisel saadi kõrgem enantioselektiivsus (kuni 77%). Leiti, et katalüütilise süsteemi aktiivsus ja stereoselektiivsus on sõltuv mitmetest faktoritest (nagu temperatuur, katalüsaatori komponentide moolvahekord ja substraadi kontsentratsioon).

Antud tööga on näidatud, et *3S,3´S*-bimorfoliin on perspektiivne ligand metall-katalüütiliste reaktsioonide jaoks.

CONTENTS

1. LIST OF PUBLICATIONS

This thesis is based on the following articles referred to in the text by Roman numbers.

I Kriis, K.; Kanger, T.; Pehk, T.; Lopp, M. Synthesis of (2*S*,2´*S*)-bimorpholine. *Proc. Estonian Acad. Sci. Chem.* **2001**, *50*, p. 173-179.

II Kanger, T.; Kriis, K.; Pehk, T.; Müürisepp, A.-M.; Lopp, M. Asymmetric synthesis of novel C_2-symmetric bimorpholines. *Tetrahedron: Asymmetry* **2002**, *13*, p. 857-865.

III Kriis, K.; Kanger, T.; Müürisepp, A.-M.; Lopp, M. C_2-symmetric bimorpholines as chiral ligands in the asymmetric hydrogenation of ketones. *Tetrahedron: Asymmetry* **2003**, *14*, p. 2271-2275.

2. ABBREVIATIONS

*	chiral
AD-mix-β	asymmetric dihydroxylation catalyst
BINAP	2,2´-bis(diphenylphosphino)-1,1´-binaphthyl
Boc	*tert*-butoxycarbonyl
Cbz	benzyloxycarbonyl
cod	1,5-cyclooctadiene
DEAD	diethyl azodicarboxylate
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
hd	1,5-hexadiene
L	ligand
LG	leaving group
M	metal or certain metallic precursor (like $[Rh(cod)Cl]_2$ dimer)
Ms	methanesulfonyl
NMR	nuclear magnet resonance
Ns	*p*-nitrobenzenesulfonyl
r.t.	room temperature
R_L	larger group
R_S	smaller group
S	substrate
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	*p*-toluenesylfonyl
UV	ultra violet
vs	*versus* – compared

3. INTRODUCTION

Needs for enantiomerically pure compounds in the pharmaceutical, agrochemical or cosmetic industry is permanently growing. As a result, it generates a growing importance of the methods obtaining those compounds.

Three possible strategies exist for enantiomeric compounds production: use of natural chiral starting compounds (use of "chiral pool"), resolution of racemic mixtures obtained from ordinary organic synthesis and direct asymmetric synthesis.[1] Each of these alternatives has its own advantages and disadvantages. So the choice depends on each specific case, e.g. if both enantiomers of a certain compound are needed for biological evaluation, the resolution of a racemic mixture may be the method of choice. When one enantiomer of a compound is needed in bulk quantities, then the chemical synthesis of racemic mixtures followed by their resolution into antipodes is disadvantageous because of environmental, economical and toxicity reasons. Historically, the dominating method of production of optically active compounds was the isolation of those from natural sources followed by further transformations.

Asymmetric synthesis has been defined as a reaction (or sequence of reactions) that creates a new stereogenic unit in a controlled way [2]. The chirality of a new product may be induced by stereogenic centre already existing of the substrate, chiral reagent, chiral auxiliary or ligand of a metal complex. Based on these specific features, the asymmetric synthesis may be divided into four "generations".

The first-generation asymmetric synthesis means the diastereoselective reactions where an existing stereogenic centre generates a new centre in the same molecule (a substrate-controlled asymmetric synthesis).

The second-generation asymmetric synthesis refers to the asymmetric induction controlled by the stoichiometric amount of a chiral auxiliary, which is covalently bonded to the substrate (an auxiliary-controlled asymmetric synthesis).

The third-generation asymmetric synthesis is a process where the stoichiometric amount of a chiral reagent effects asymmetric induction (a reagent-controlled asymmetric synthesis).

The fourth-generation asymmetric synthesis includes catalytic modifications of the second- and third-generation methods. The catalytic amount of chiral auxiliary or ligand (as a component of metal-catalyst) induces the new stereogenic centre to the substrate. It might act in an intermediate of the catalytic cycle or in an intermolecular fashion in a single step (a catalytic asymmetric synthesis).

Generally, in chiral ligands preparation the use of natural chiral starting compounds is predominant. It is the most inexpensive way as the "chiral pool" as a source of available asymmetric material is cheap. Moreover, in most cases, it is also the simplest and the shortest strategy. The chiral heteroatom-containing compounds with good chelating properties are most suitable for further application in the asymmetric metal-catalysed reactions.

Thus, in the present work we had two main goals: first, to synthesise two new chiral *N,O*-containing bicycles - *2S,2´S*- and *3S,3´S*-bimorpholine, and, secondly, to study their influence as chiral ligands on the asymmetric transfer hydrogenation of prochiral aromatic ketones. Based on these goals, the first part consists of the literature survey that describes the synthesis of *N,O*- or *N*-containing bicyclic molecules using "chiral pool", resolution of racemate or direct asymmetric synthesis. We also focused on the ring-closure reactions, as it

is the most important step in the synthesis of heterocycles. The first part includes our own studies towards the synthesis of *2S,2′S*- and *3S,3′S*-bimorpholine, with the results discussed.

The second part is devoted to the asymmetric transfer hydrogenation of ketones, a fourth-generation asymmetric reaction. The literature survey covers the use of different heteroatom-containing ligands in this reaction. This part includes also our first results using the newly synthesised (Part I) chiral C_2-symmetric bimorpholines as chiral ligands in the asymmetric transfer hydrogenation of ketones.

4. Part I
C_2-SYMMETRIC HETEROATOM-CONTAINING BICYCLES

C_2-symmetric heteroatom-containing compounds have been extensively used as valuable ligands in many asymmetric transformations [3]. The chiral pool serves an outstanding and inexpensive source of asymmetric material for synthesis of these compounds. However, several catalytic and stoichiometric asymmetric syntheses procedures are also known. Despite abundance of methods provided by asymmetric synthesis, some of these compounds are obtained by resolution of racemates. There are no simple and versatile universal methods for preparation of chiral molecules; each case has own optimal solution.

Why are C_2-symmetric heteroatom containing compounds so valuable synthons in asymmetric synthesis? The combination of C_2-symmetry and the position of heteroatoms in the chiral ligand can lead to the conformational restriction in the chelation with metal, which increases the stereodifferentiation for various metal mediated reactions. The structural rigidity of the different chiral heterocycles increases effectiveness using them in the asymmetric reactions. They can cause an efficient chirality transfer from the heterocycle to the newly formed bonds, thereby generating new stereogenic centers with high asymmetric induction.

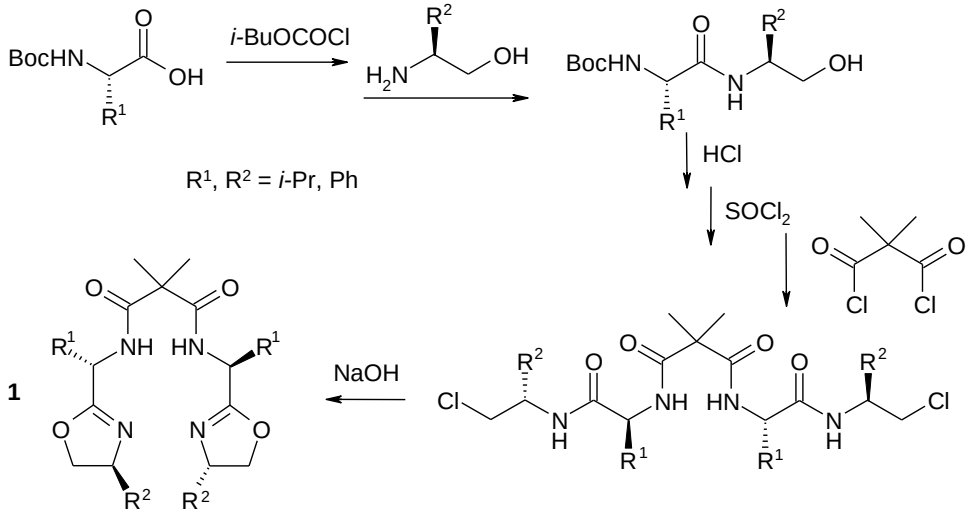
Based on these positive properties, the preparation of chiral C_2-symmetric *N*,*O*- and *N*-containing heterocycles has become one of important areas in the organic synthesis. Most attention is turned to preparing of C_2-symmetric bisoxazolines (a recent review [4]); but only few examples are known about synthesis of bisoxazolidines [5,6]. Despite numerous studies describing the synthesis of saturated nitrogen heterocycles (reviews [7,8,9,10]), there is little information about the synthesis of C_2-symmetric bridged heterocycles, like bipyrrolidines [11,12,13] and bipiperidines [14]. At the same time, C_2-symmetric bisaziridines have found to be attractive subjects [15]. Several applications of the synthesis of conformationally restricted [16,17,18] and flexible bisaziridines [19,20,21] are known. More detailed information about the synthesis of such kind heteroatom-containing bridged cycles is presented in the following sections.

4. 1. Synthesis of enantiomeric C_2-symmetric *N,O*- or *N*-containing bridged heterocycles

4. 1. 1. Different strategies for the introduction of chirality

For the synthesis of enantiomerically pure C_2-symmetric *N,O*- or *N*-containing bicyclic derivatives, all above-mentioned ways for the introduction of chirality are employed. The most popular strategy is based on the use of "chiral pool" as available and inexpensive source of asymmetric material. Chiral amino alcohols, tartaric acid and sugar derivatives are the most widely used starting materials.

The syntheses of bisoxazolines follows a general synthetic route, which starts from the condensation of a dicarboxylic acid derivative with an optically active 1,2-amino alcohol [22,23,24,25]. Also, the conformationally constrained bisoxazolines were synthesised by using of chiral 1,2-amino indanol [26,27]. The required enantiomerically pure amino alcohols are either commercially available or could be easily prepared by reduction from the corresponding α-amino acids [28]. The structure of bis(oxazoline) derivatives can be easily modified by the variation and combination of either a dicarboxylic acid, an amino acid or an amino alcohol. Adolfsson et al. have designed an interesting series of C_2-symmetric tetradentate bisoxazolines **1** based on the combination of commercially available enantiomerically pure starting materials, like amino alcohols and amino acids (Scheme 1. *N*-Boc protected *L*-valine or (*R*)-phenylglycine was coupled with (*S*)-valinol or (*R*)-phenylglycinol) [29].

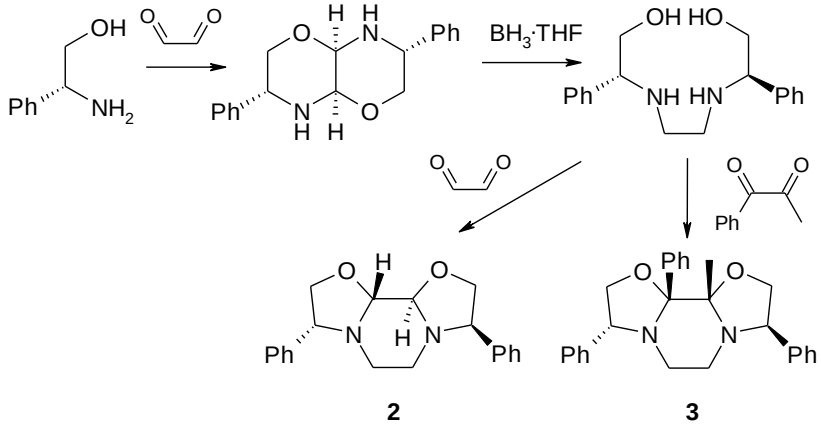


Scheme 1. Synthesis of C_2-symmetric tetradentate bisoxazolines

Andersson has reported the synthesis of new class bisoxazolines where two oxazolines are separated by a tartrate backbone [30]. For the synthesis of chiral bisoxazolidines the enantiomerically pure amino alcohols are also used [5].

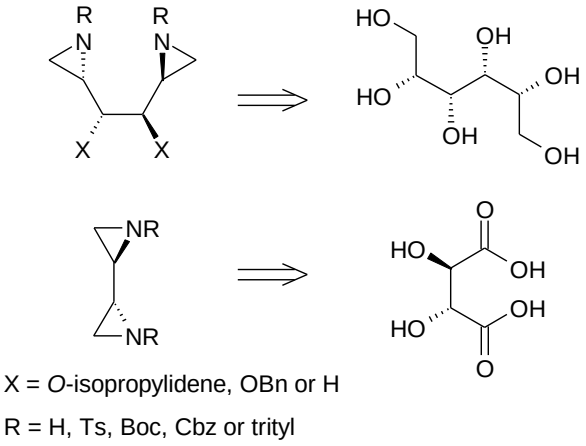
Without doubt, such strategy for preparing of bis(oxazoline) and -(oxazolidine) derivatives is the best one – the most inexpensive from the part of the reagent cost, the simplest from the part of chemical transformations and the shortest. In addition to this strategy, there is an example where an enantiomerically pure amino alcohol is used, but it is affected in the substrate-controlled way. Farfan et al. have widely studied the condensation of amino alcohols with α-diketones [31]. These reactions proceed with remarkable regio- and

stereoselectivity, to provide a wide variety of products (among them also bisoxazolidines **2** and **3**). Also, the reactions strongly depend on the reaction conditions as well as the nature of reagents (Scheme 2).



Scheme 2. Synthesis of chiral bisoxazolidines by stereoselective condensation

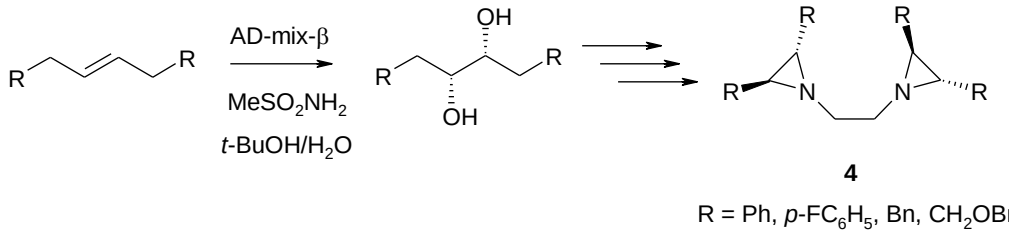
The studies describing the synthesis of chiral *N*-containing bridged heterocycles are also starting from the enantiomerically pure compounds from "chiral pool". Several syntheses of enantiopure bisaziridines use *D*-mannitol as readily available chiral starting material [16,19,32] and some authors (including our laboratory) have developed synthetic methods starting from tartaric acid [17,18] (Scheme 3).



Scheme 3. Enantiomeric natural products as starting materials for C_2-symmetric bisaziridines

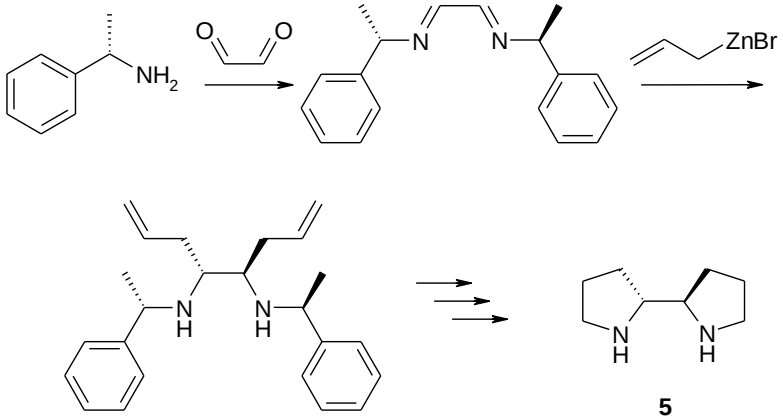
Kotsuki et al. have described the synthesis of chiral C_2-symmetric bipyrrolidine derivatives starting from mannitol or tartaric acid [12].

However, in addition to numerous examples of using "chiral pool" as a starting material, there is a couple of synthetic routes containing direct asymmetric synthesis. One of them is described by Tanner and Andersson [20,21]. Their strategy to synthesise various flexible bisaziridines **4** is based on the Sharpless asymmetric *cis*-dihydroxylation of alkenes [33,34] (Scheme 4).



Scheme 4. Synthesis of C_2-symmetric bisaziridines starting by Sharpless asymmetric *cis*-dihydroxylation

A second example shows the use of an enantiomerically pure compound in an auxiliary-controlled way. Alexakis et al. [13] have developed a short way to synthesise (*R*,*R*)-2,2′-bipyrrolidine **5** (shorter if compare that of described by Kotsuki [12]). This alternative strategy allows generating of two new stereogenic centres by using enantiomerically pure ethylphenylamine as auxiliary [35] (Scheme 5).



Scheme 5. Synthesis of (*R*,*R*)-2,2′-bipyrrolidine

An advantage of this synthetic route is its possible use in a large scale. All diamine derivatives of this synthetic strategy are purified by a simple acid-base washing procedure to give a quantitative yield of a material suitable for further transformation.

In addition to above-mentioned routes, there are some examples where enantiomeric heterocycles are obtained via resolution of racemate. Hirama has reported the first preparation of C_2-symmetric bipyrrolidine derivative in this way [36]. They started from the readily available 2,2′-(1′-pyrrolinyl)pyrrole and separated the obtained racemic bipyrrolidine with *D*-tartaric acid. Later Hirama and co-workers have described an improved procedure by shortening the synthesis to the three steps [11]. In spite of this synthetic route provides both enantiomers in optically pure form, the alternative strategy described by Alexakis [13] has its own advantage, such as a better yield (19% versus 61% overall yield, respectively).

The preparation of optically pure (*R*,*R*)-2,2′-bipiperidine by resolution of racemic form through its cobalt-complex is described by Yoshikawa [14]. To our knowledge, this is the single report about synthesis of optically pure 2,2′-bipiperidine.

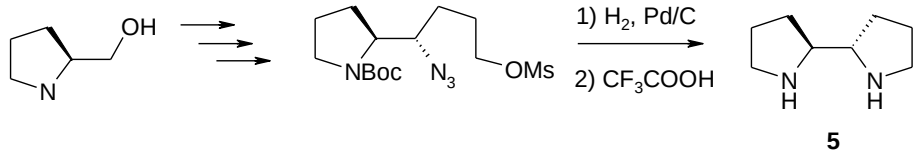
4. 1. 2. Cyclisation methods for the synthesis of *N*,*O*- or *N*-containing bridged heterocycles

4. 1. 2. 1. Reductive cyclisation of azide derivatives

The reduction of the azide function in the presence of displaceable functionalities (such as carbonyl or activated hydroxyl groups) in the same molecule affords access to nitrogen heterocycle [37].

Thus, hydrogenation of azido aldehyde in the presence of 10% Pd/C led to the formation of the cyclic secondary amine [38]. This conversion requires reduction of the azido group to an amine and subsequent intramolecular reductive cyclisation of the amino aldehyde.

Azido alcohol could not be cyclised in one-step procedure, but its conversion to the azido tosylate led to the spontaneous cyclisation in the reductive conditions [39]. Among several possibilities to prepare *N*-containing bridged heterocycles, only one of those conditions is followed: Hirama and Masamune have reported preparing of (*S*,*S*)-2,2′-bipyrrolidine **5** from (*S*)-2-pyrrolidinemethanol [11]. Cyclisation is accomplished by the reduction of azide functionality in the presence of a good leaving group in the same molecule that leads to the ring-closure (Scheme 7).

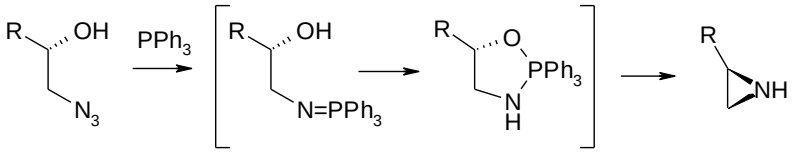


Scheme 7. Synthesis of (*S*,*S*)-2,2′-bipyrrolidine

Staudinger reaction

One of the mildest and most selective ways to reduce azido group is to use triphenylphosphine, which forms a corresponding iminophosporane intermediate. Numerous articles have appeared describing the use of this method for the construction of nitrogen containing heterocycles [40].

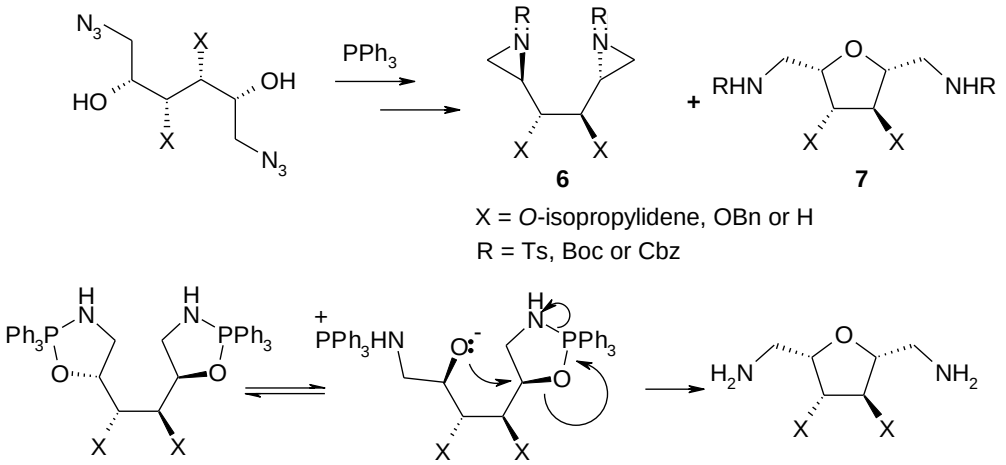
Staudinger reaction is one of the most widely used methods for the synthesis of aziridines from 2-azido alcohols. This conversion is believed to proceed via an initial formation of iminophosphorane. The intramolecular nucleophilic attack of hydroxy groups leads to a cyclic intermediate. Subsequent elimination of triphenylphosphine oxide affords an aziridine with inversion of absolute configuration (Scheme 8).



Scheme 8. Stereospecific synthesis of aziridine

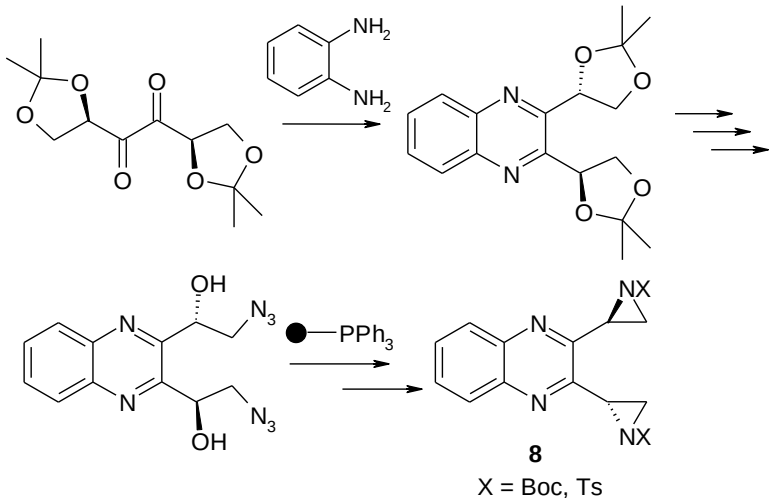
Several syntheses of various C_2-symmetric bisaziridines via the above-mentioned route started from *D*-mannitol or tartaric acid [16-19,32]. The reaction of conformationally flexible diazidodiols (X = H or OBn) with triphenylphosphine led to the mixture of the corresponding bisaziridines and tetrasubstituted furans [19], both derivatives were isolated in their *N*-protected

forms **6** and **7**. The formation of furans could result from a competitive thermal decomposition of the intermediate oxazaphospholidine, allowed by the flexibility of carbon chain (Scheme 9).



Scheme 9. Synthesis of C_2-symmetric bisaziridines by Staudinger reaction

Recently McCort et al. reported a synthesis of conformationally semi-rigid bisaziridines **8** bridged with an aromatic ring [32]. A *D*-mannitol derived diketone was the precursor, which gave the quinoxaline derivative by the coupling with 1,2-phenylenediamine. The crude bisaziridine was formed in a quantitative yield by the reductive aminocyclisation followed by the protection of the nitrogen unit (Scheme 10). It is the first time when a polymer-supported triphenylphosphine was used in the Staudinger reaction.

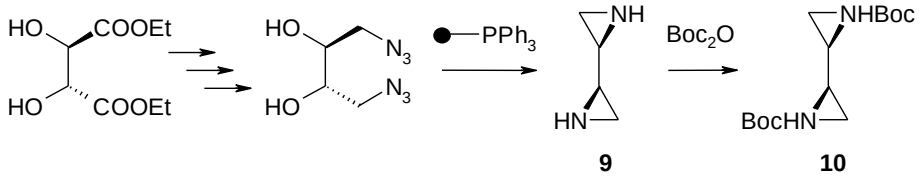


Scheme 10. Synthesis of bisaziridines with polymer-supported triphenylphosphine

Also, other authors started the synthesis of C_2-symmetric bisaziridines from tartaric acid using the Staudinger reaction. So, *L*-tartaric acid was converted into diazidodiol according to the literature procedures, followed by the transformation of the product into bisaziridine by treatment with triphenylphosphine [17]. However, the isolation of the target compound was unsuccessful. Therefore, bisaziridine was derivatised with trityl chloride, affording a crystal *N*-protected compound, but even then the obtained yield was very low.

Recently, in our laboratory, two synthetic routes for the preparation of Boc-protected bisaziridine from tartaric ester were developed [18]. One of them is based on the use of polymer-

supported triphenylphosphine, affording also unprotected bisaziridine **9** (Scheme 11). Boc-protected 2,2′-bisaziridine **10** was synthesised with a high yield and in high enantiomeric purity.

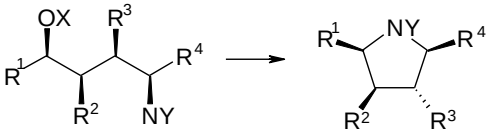


9 **10**

Scheme 11. Synthesis of restricted C_2-symmetric bisaziridine from tartaric ester

4. 1. 2. 2. Direct cyclisation of amino alcohol derivatives

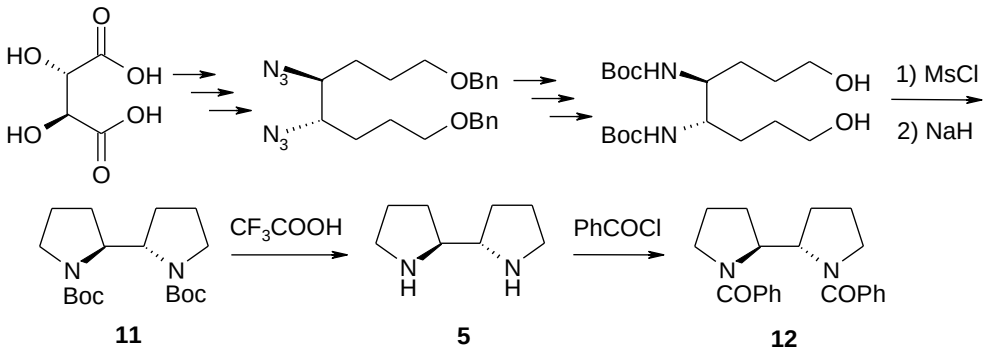
Many examples of the syntheses of functionalised pyrrolidines by intramolecular S_N2 reaction from amino alcohol derivatives are described in the literature [8]. Cyclisation is usually stereospecific and a very little amount of epimerisation occurs during this process (Scheme 12).



OX = leaving group

Scheme 12. Stereospecific cyclisation of aminoalcohol derivatives

This method of cyclisation was used to prepare C_2-symmetric bipyrrolidine derivatives. Kotsuki et al. have reported a synthesis of the above-mentioned compounds, starting from mannitol or tartaric acid [12]. The route that started from *D*-tartaric acid is outlined in Scheme 13. Catalytic hydrogenation of the azido groups afforded diamine, which was protected with Boc_2O. After debenzylation and mesylation of hydroxy groups the intramolecular cyclisation of the obtained substrate led to Boc-protected bipyrrolidine **11**. The corresponding free bipyrrolidine **5** was obtained via deprotection by the acid-base treatment. Further benzoylation was used to obtain a stable crystalline *N*-protected bipyrrolidine **12**.

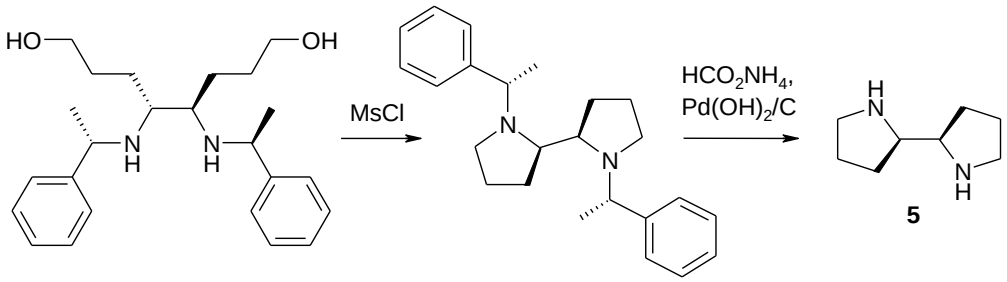


11 **5** **12**

Scheme 13. Synthesis of 2,2′-bipyrrolidine by intramolecular S_N2 attack

Exactly the same synthetic sequence from *L*-tartaric acid was used in order to obtain the other enantiomer of 2,2′-bipyrrolidine **12**.

Alexakis et al. have developed an alternative shorter way to (*R*,*R*)-2,2′-bipyrrolidine **5** [13], starting from enantiomerically pure ethylphenylamine and glyoxal (see Section 4. 1. 1., Scheme 5). Subsequent hydroboration of the obtained diamine gave the corresponding diol, the cyclisation of which was carried out in one step simultaneously with the mesylation. The debenzylation of the amino groups with Pearlmann′s catalyst led to (*R*,*R*)-2,2′-bipyrrolidine **5** (Scheme 14).



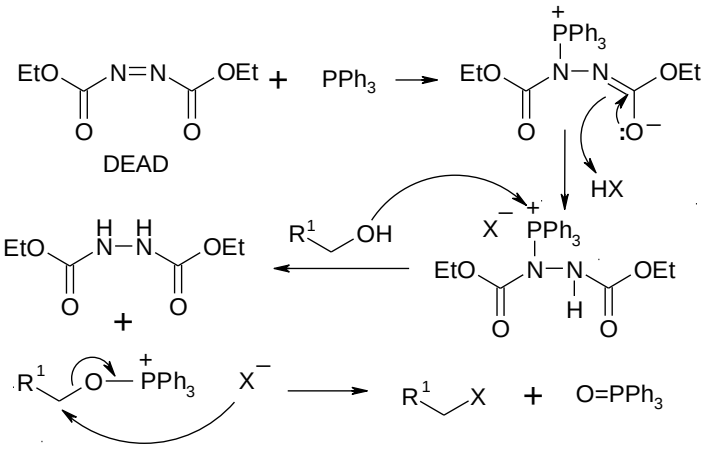
Scheme 14. Preparation of 2,2′-bipyrrolidine by stereospecific cyclisation

To prepare Boc-protected bisaziridine **10** from tartaric ester, two synthetic routes were developed in our laboratory [18]. One of them mentioned in Section 4. 1. 2. 1. uses the Staudinger reaction. Another possibility is based on the direct cyclisation of *N*-Boc protected dimesylate by treatment with sodium hydride (Scheme 15). The other enantiomer of bisaziridine **10** was also prepared from (*S*,*S*)-tartaric ester according to the same scheme. The use of this method allows synthesising Boc-protected 2,2′-bisaziridines with a high yield and excellent enantiomeric purity.

Scheme 15. Synthesis of Boc-protected bisaziridine

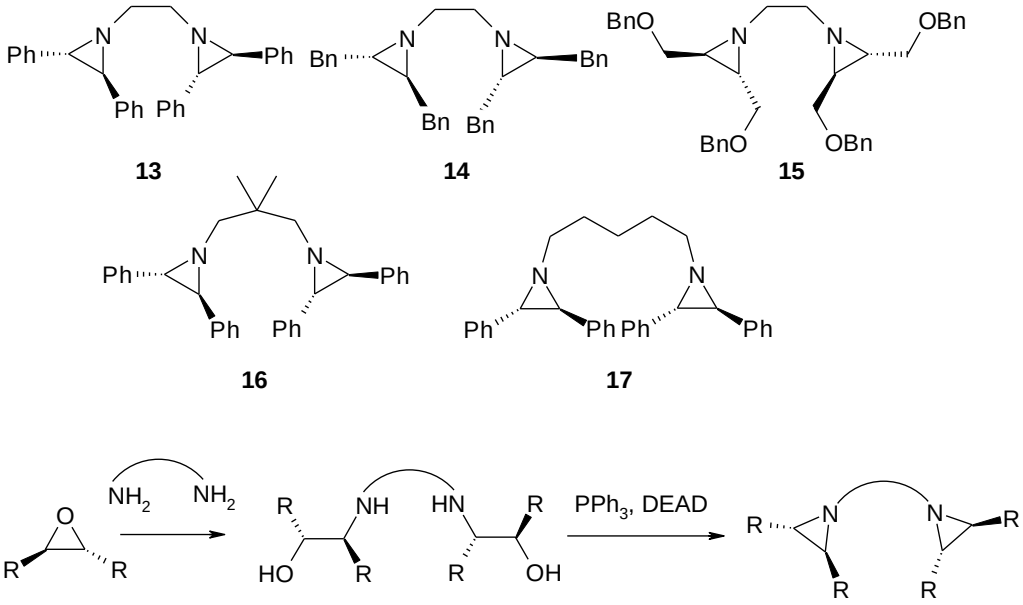
Mitsunobu reaction

In general, Mitsunobu reaction is a versatile method for the alkylation of various nucleophiles with alcohols, using the redox system of diethyl azodicarboxylate (DEAD) and triphenylphosphine [41] (Scheme 16). In this way, a poor leaving group is converted into a good leaving group in the intermediate and the reaction occurs even when the nucleophile is comparably weak.



Scheme 16. Mechanism of Mitsunobu reaction

Mitsunobu reaction is one of the widely used cyclisation methods. The asymmetric synthesis of various flexible bisaziridines **13** – **17** (Scheme 17) based on the cyclisation by Mitsunobu reaction is described by Tanner and Andersson [20,21]. They have used a synthetic strategy, which started with the Sharpless asymmetric *cis*-dihydroxylation (see Section 4. 1. 1., Scheme 4) followed by epoxidation. Further ring-opening reaction of epoxide by a suitable diamine gives the corresponding diamino diol, which is cyclisised in the double Mitsunobu reaction to the desired bisaziridine.



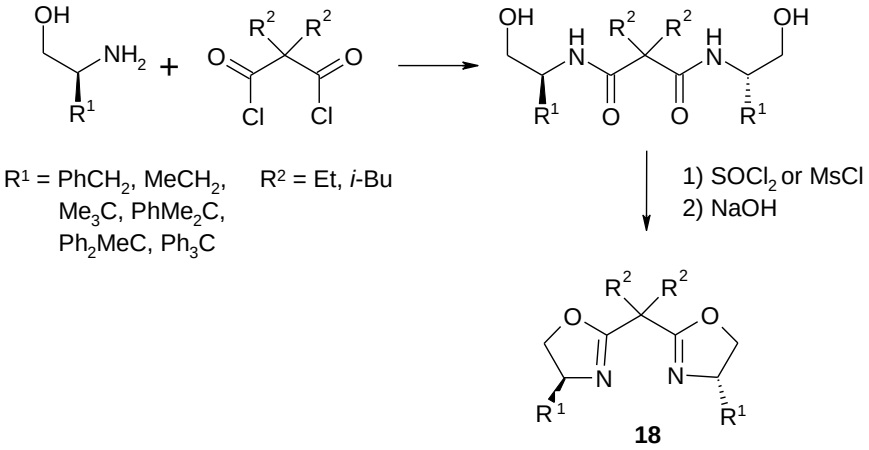
Scheme 17. General strategy for synthesis of various flexible bisaziridines **13**-**17**

This strategy is flexible and allows for a variation of substituents in the aziridine-ring and different lengths of the tether.

4. 1. 2. 3. Cyclisation of activated hydroxyamides

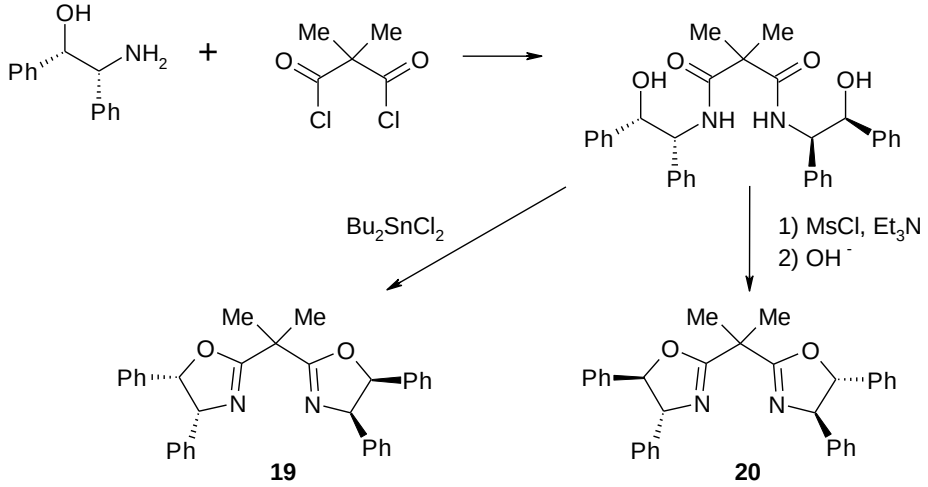
The syntheses of bisoxazolines proceed via cyclisation of activated hydroxyamides. For this purpose, hydroxyl groups in the bis(hydroxy)amide are activated and the resulting intermediate is cyclisised to provide the bis(oxazoline) derivative. The major difference between those processes is only the use of different activating agents [4].

Denmark et al. have reported the synthesis of enantiomerically pure 4-substituted bisoxazolines **18** from chiral amino alcohols and malonyl dichloride derivatives [23] (Scheme 18). The hydroxyl groups were activated either with thionyl chloride or by formation of the bismesylate followed by cyclisation with an aqueous or alcoholic base.



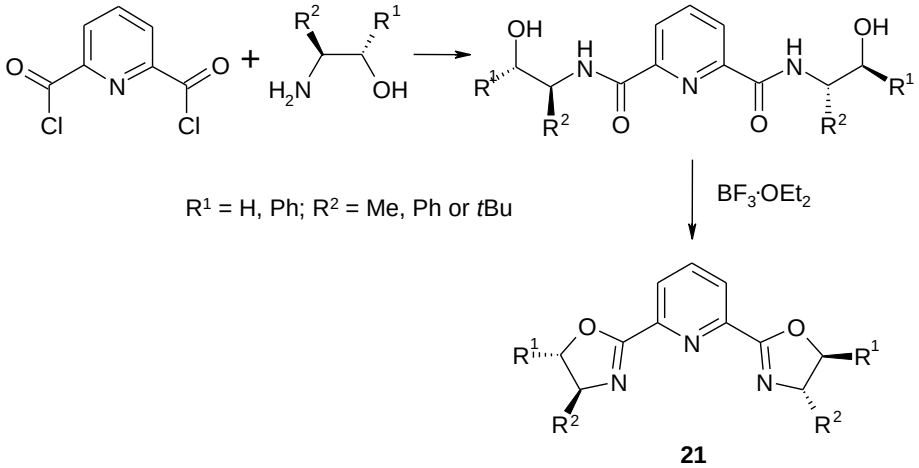
Scheme 18. Synthesis of chiral 4-substituted bisoxazolines

Desimoni and co-workers have described a stereodivergent synthesis of chiral 4,5-disubstituted bisoxazolines [24]. The use of optically active 1,2-disubstituted amino alcohol allowed getting either *cis*- or *trans*-4,5-disubstituted bisoxazolines **19** and **20** (Scheme 19). Depending on the cyclisation conditions, either retention or inversion of configuration at the C-5 position occurred. In the presence of dichlorodibutyl stannane *cis*-4,5-disubstituted bisoxazolines **19** was obtained, while in the case of bismesylate followed by treatment with the base the reaction product was the *trans*-4,5- disubstituted bisoxazolines **20**.



Scheme 19. Stereodivergent synthesis of chiral 4,5-disubstituted bisoxazolines

Davies et al. has presented a synthesis of tridentate bis(oxazolinyl)pyridines starting from pyridine-2,6-dicarboxylic acid chloride (Scheme 20) [27]. In that case, the cyclisation of bis(hydroxy)amides by treatment with $BF_3{\cdot}OEt_2$ afforded bis(oxazolinyl)pyridines **21** (pybox ligands) in good yields. This reagent allows also synthesising the constrained pybox ligands derived from *cis*-1,2-amino indanol with the retention of the configuration.

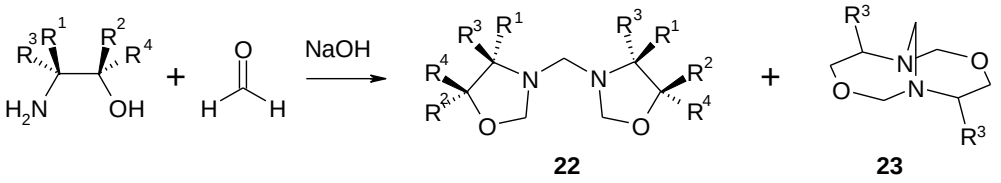


Scheme 20. Synthesis of tridentate bis(oxazolinyl)pyridines

4. 1. 2. 4. Condensation as method for the ring-closure

Oxazolidines have been usually obtained by condensation of carbonyl compounds with amino alcohols in a 1:1 ratio. However, only a few examples describe the synthesis of the chiral bis(oxazolidine) derivatives (see also Section 4. 1. 1., Scheme 2).

Bolm and co-workers have reported the synthesis of optically active C_2-symmetric *N,N´*-methylenebisoxazolidines [5]. Treatment of chiral amino alcohols with an excess of formaldehyde followed by the cyclisation-reaction in basic conditions provided *N,N´*-methylenebisoxazolidines **22** (Scheme 21). In fact, depending on the nature of the amino alcohol, condensation may give a mixture of different products (two products **22** and **23** were obtained in 2:1 ratio, respectively, when R^3 =Ph; R^1, R^2, R^4 = H).



Scheme 21. Synthesis of chiral C_2-symmetric *N,N´*-methylenebisoxazolidines

Summary

In summary, this short review shows that the use of "chiral pool" is the dominating method in the synthesis of chiral C_2-symmetric *N,O*- and *N*-containing bicycles. Only a couple of synthetic routes containing a direct asymmetric synthesis were described and typically expensive chiral reagents are needed for that purpose. Also, the asymmetric induction of a chiral reagent (chiral auxiliary or catalyst) usually depends on the structure of

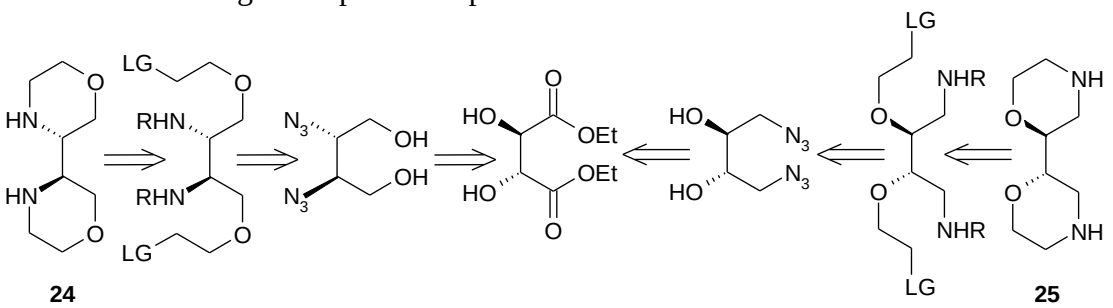
the substrate. None of direct asymmetric reactions are universal. The resolution of the racemate as a method for the preparation of enantiomeric heteroatom containing bicycles is also described only in two cases. Despite a common quite short synthetic route, the resolution of racemic mixture affords enantiomers in a comparable low yield. Thus, the use of a natural chiral product with further chemical transformations seems to be the best choice.

In the previous sections some of the cyclisation methods were described to demonstrate the synthesis of C_2-symmetric *N*,*O*- and *N*-containing bicycles. However, from these data it is not clear which is the most efficient and selective for the construction of bimorpholines.

5. GOALS OF THE PRESENT STUDY

C_2-symmetric heteroatom-containing compounds as chiral ligands have been extensively used in various catalytic processes. Increasing interest in C_2-symmetric cyclic diamines where nitrogen is included into the cycle has encouraged us to study the synthesis of chiral C_2-symmetric bimorpholines. The short overview above shows the possibilities already used to synthesise such bridged heterocyclic derivatives. The need of a cyclisation method is self-evident and the literature offers a wide variety of them.

Our general strategy for the synthesis of C_2-symmetric bimorpholines is outlined in Scheme 22. We have chosen (*R*,*R*)-tartaric acid ester as a very convenient precursor (its enantiomer is also commercially available) and according to this general scheme the preparation of both target compounds is possible.



Scheme 22. Retrosynthetic route for the C_2-symmetric bimorpholines

The scheme consists of three major steps:

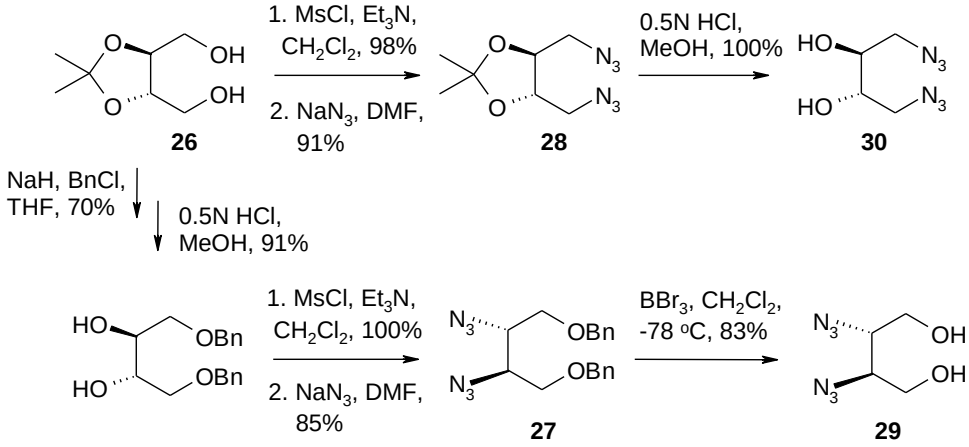
- to introduce the nitrogen-containing functionality into the tartaric acid derivative
- to construct an appropriately substituted intermediate via *O*-alkylation of hydroxyl groups with a functionalised C2 unit
- to find a method for the ring-closure process

6. SYNTHESIS OF (2*S*,2´*S*)- AND (3*S*,3´*S*)-BIMORPHOLINE
Results and discussion

6. 1. Introduction of the nitrogen-containing functionality (Article I)

We started the synthesis from commercially available diol **26**, which is a simple (*R*,*R*)-tartaric acid derivative. Nitrogen-containing functionality was introduced by the transformation of hydroxyl groups into azido groups. It was carried out by a standard method involving conversion of diol **26** into dimesylate, which is the most commonly employed sulfonate leaving group, and subsequent azide ion displacement [37]. The synthesis of diazide **27** requires previous protection of hydroxyl groups in diol **26** (for discrimination between primary and secondary hydroxyl groups) followed by deacetalisation in acidic conditions (Scheme 23). The corresponding diazides **27** and **28** were obtained in good yield 85% and 89%, respectively (for two steps: mesylation and azidation). Further deprotection of hydroxyl groups led to diazido diols **29** and **30**.

The synthesis of diazide **27** proceeded with the inversion of the configuration of the stereogenic centres. It can be considered as a mechanism-controlled reaction. S_N2 displacement is a good example of such reactions [42].



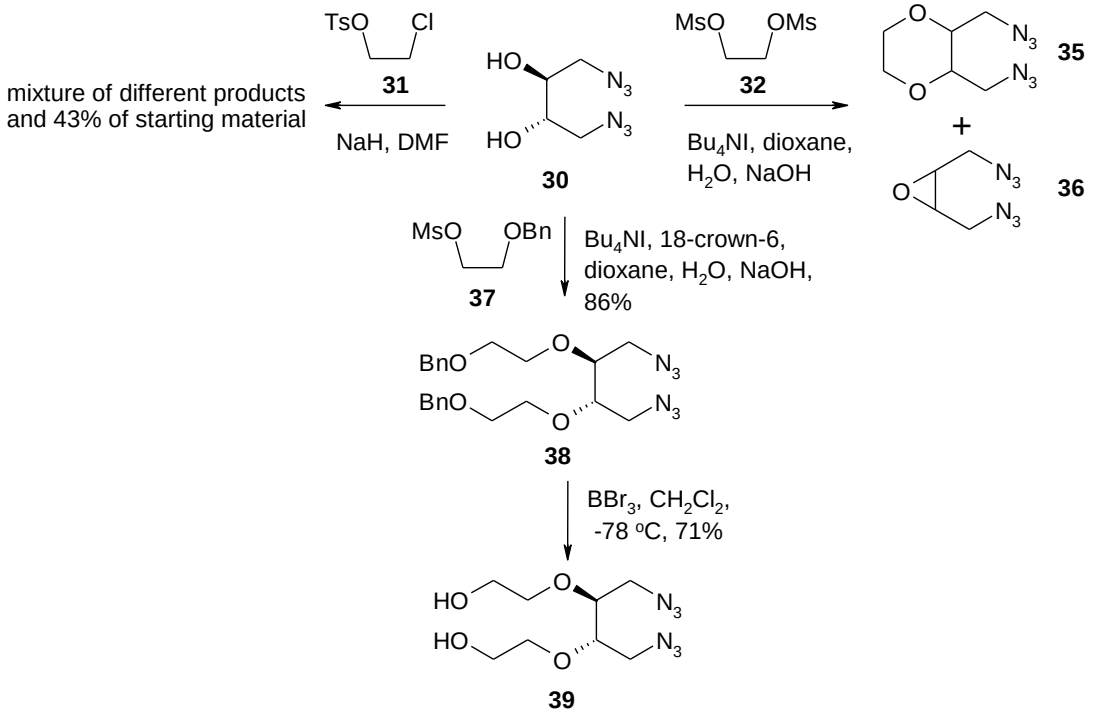
Scheme 23. Introduction of the *N*-containing functionality into the (*R*,*R*)-tartaric acid derivative

We have also improved the synthetic pathway for (3*S*,3´*S*)-bimorpholine **24** by changing the sequence of the nitrogen introduction and the elongation of the chain by *O*-alkylation with C2 unit (will be discussed in the next chapter, Scheme 25; Article II).

The transformation of hydroxyl groups into azido groups in order to introduce the *N*-containing functionality into (*R*,*R*)-tartaric acid derivative is a very convenient method for this purpose. The use of intermediate compounds **27** and **28** allows controlling of the configuration of the stereogenic centres of the target bimorpholines.

6. 2. *O*-alkylations (Article I, II)

The elongation of the carbon chain with the C2 unit was not trivial and caused problems (Article I): use of either the commercially available 2-chloroethyl *p*-toluenesulfonate **31** or dimesylate **32** easily available failed (Scheme 24).

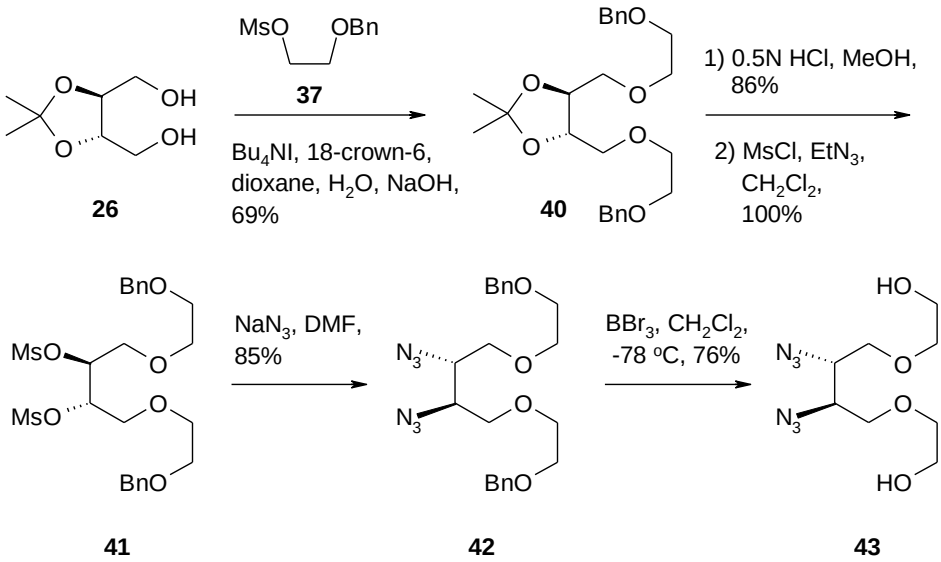


Scheme 24. Examination of different *O*-alkylating reagents

The reaction of diol **30** with 2-chloroethyl *p*-toluenesulfonate **31** afforded a mixture of different products and almost half of the starting material was recovered. Two hardly separable cyclic products **35** and **36** (in 1:1 ratio) were afforded by using dimesylate **32**. The formation of **35** can be expected; the formation of **36** could be explained supposing esterification of the released methanesulfonic acid with diazido diol **30** followed by intramolecular S_N2 attack.

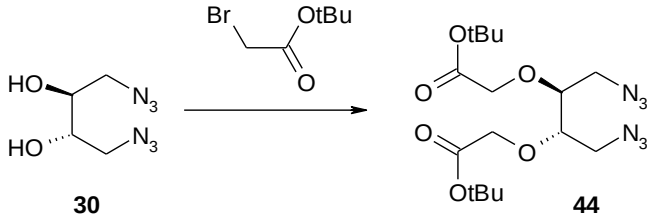
We succeeded in obtaining the required transformation under phase transfer conditions with monoprotected ethylene glycol mesylate **37**, followed by cleavage of benzyl groups in the intermediate compound **38** (Scheme 24). Alkylating reagent **37** was synthesised in two steps from ethylene glycol. The monoprotection with benzyl bromide followed by the mesylation of another hydroxyl group afforded the desired product.

An analogous method was used for *O*-alkylation in the synthesis of (3*S*,3´*S*)-bimorpholine **24**, only in the inverse sequence (Article II): diol **26** was first alkylated and after deacetalisation of the corresponding double-alkylated product **40,** the nitrogen functionality was introduced (Scheme 25). For the following ring-closure, the benzyl-protecting group in diazide **42** was removed.



Scheme 25. *O*-alkylation step and introduction of nitrogen functionality for bimorpholine **24** synthesis

Because of the best route for the elongation of the chain remained relatively labour consuming, we chose another possible synthetic route. Considering also the following cyclisation step, we supposed the reaction with *tert*-butyl bromoacetate to be a promising procedure. It is known that lactams are obtained via reductive cyclisation of azido esters [43]. So, the corresponding ester **44** was synthesised from diazido diol **30** (Scheme 26), unfortunately in a quite moderate yield (41% under unoptimised conditions). The cyclisation of compound **44** will be discussed in the next chapter.

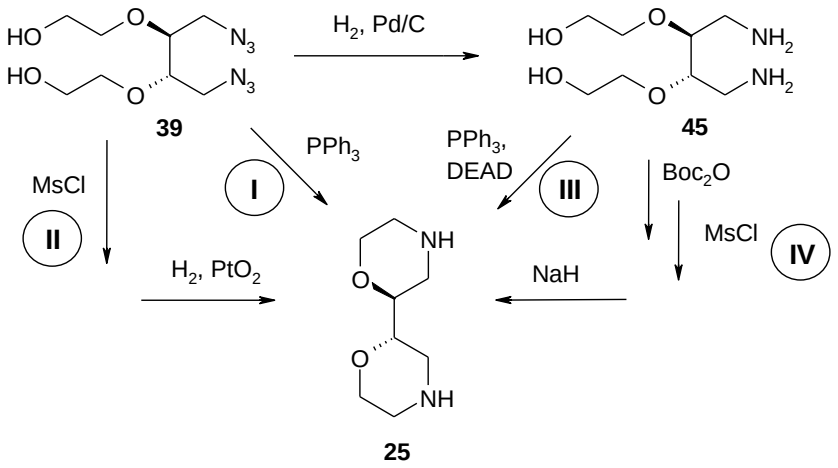


Scheme 26. Synthesis of azido ester **44**

Despite the relatively labour consuming construction of the C_2-symmetric intermediates **39** and **43** with appropriately elongated chains, we succeeded in synthesising these compounds with an acceptable yield. Also, another possible way to the synthesis of azido ester **44** was developed. Thus, two of the goals of the synthesis of bimorpholines, to construct an appropriately substituted intermediate containing *N*- and *O*-functionalities were realised.

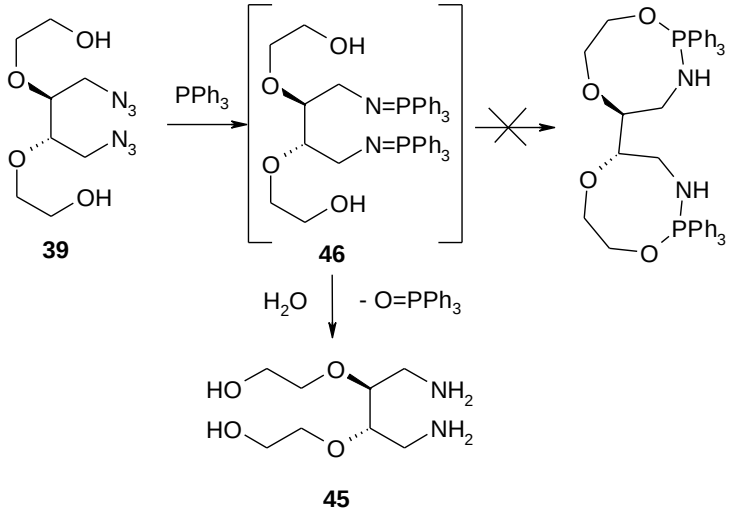
6. 3. Intramolecular cyclisations (Article I, II)

A number of methods have been used for intramolecular cyclisation in order to obtain heterocycles. In the present study, we have used only some of them also discussed in the literature survey (Section 4. 1. 2.). In scheme 27, four alternative possibilities to the cyclisation are presented.



Scheme 27. Alternative methods for cyclisation

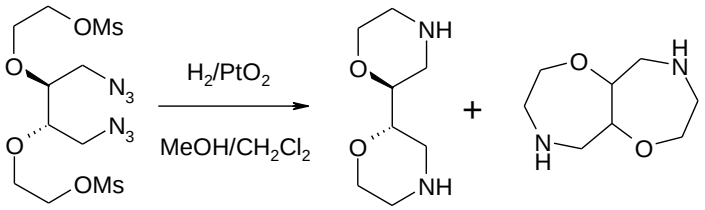
At first we tried the Staudinger reaction as the most straightforward way to the target compound (Scheme 27, method I). Numerous synthetic studies have described the use of the Staudinger reaction to construct the nitrogen containing heterocycles [40]. It is attractive to realise the reduction of azido groups and the cyclisation in one step. However, our attempts to use triphenylphosphine for this purpose failed: diazido diol **39** was converted into the intermediate iminophosphorane **46**, but further cyclisation did not occur and the corresponding diamino diol **45** was obtained (Scheme 28).



Scheme 28. Staudinger reaction

So we looked for an alternative. Another way to realise the ring-closure step is the reductive cyclisation of compound **47,** using hydrogenation catalysts (Scheme 27, method II).

This approach requires an additional step for transformation of diol **39** into dimesylate **47**. Unfortunately, the catalytic hydrogenation with Adams´ catalyst afforded two reaction products in ratio 10:1 (Scheme 29): due to cross-cyclisation, in addition to (2*S*,2´*S*)-bimorpholine **25,** side-product **25a** (in 9% yield) was formed.

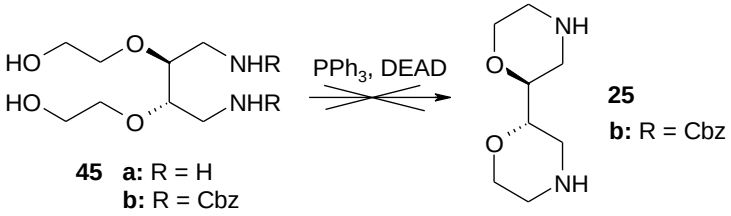


47 **25** **25a**

Scheme 29. The catalytic hydrogenation with Adams´ catalyst

Complications with separation of these products (their chromatographical behaviour is similar) prompted us to search for another and more practical synthetic route.

The Mitsunobu reaction of amino alcohols is also widely used to realise the intramolecular cyclisation (Scheme 27, method III). Several examples are known, not only with acidic *N*-compounds like Ns- and Ts-amides [44], but also with alkyl [45] or arylamines [46] and even with primary amines [47] to form heterocycles. Our attempts to use this method in constructing the bimorpholinic cycle were unsuccessful. At first, the reaction was carried out with diamino diol **45a**. The reaction did not proceed at room temperature. So, we increased the temperature (Scheme 30). Unfortunately, at elevated temperature, the decomposition of reagents occurs. The reaction using benzyl carbamate **45b** in the Mitsunobu conditions also failed (Scheme 30).

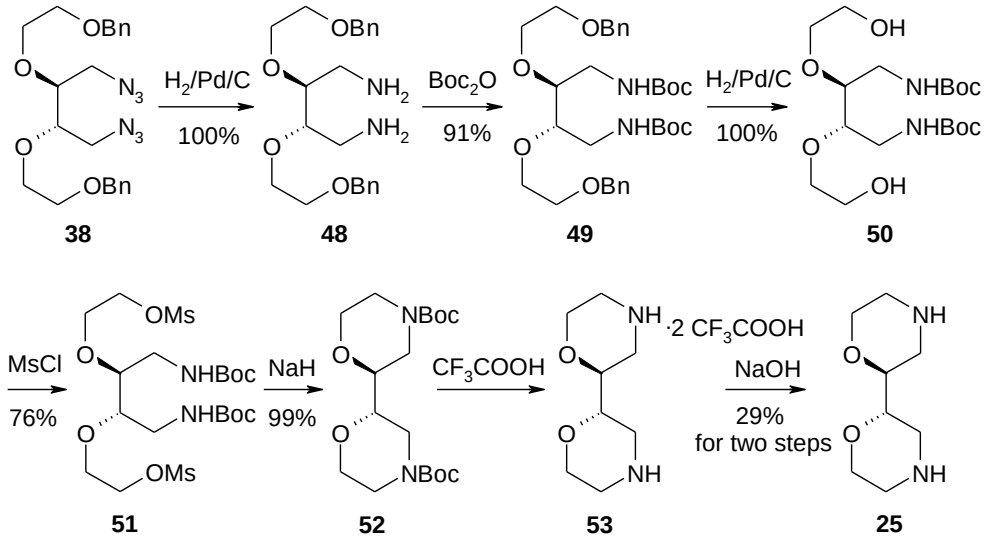


Scheme 30. The use of Mitsunobu conditions

In all the examples above, we had problems with the ring-closure: the cross-cyclisation during the reductive cyclisation (outlined in Scheme 29) and in the attempts to use the Staudinger or Mitsunobu reaction (Schemes 28 and 30). To overcome these problems we decided to modify our synthetic route and to introduce the Boc-protected intermediate (Scheme 27, method IV). Also, it makes the formed bridged heterocycle less hydrophilic and more easily isolable from the reaction mixture.

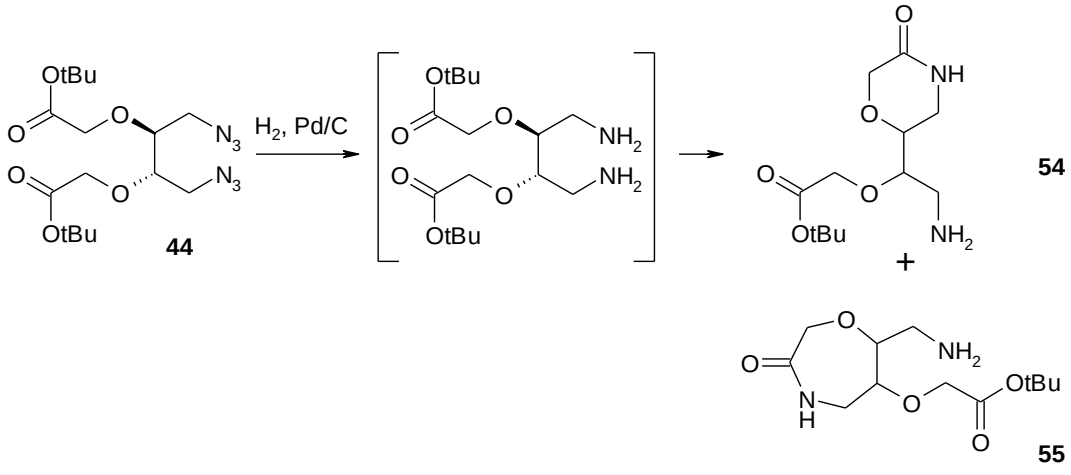
The new approach was realised in the following way: the benzyl groups were removed with BBr_3, followed by catalytic hydrogenation of the azido groups [48, 49]. Further *N*-protection with Boc_2O and addition of a good leaving group led to the suitable intermediate for the cyclisation. The reaction scheme was successfully employed (Article II). Later, we changed a couple of steps in this general synthetic scheme in order to increase the total yield of the target compounds.

Thus, diazide **38** was hydrogenated on Pd/C and the corresponding crude diamine **48** was protected with Boc_2O (Scheme 31). *N*-Boc derivative **49** allowed easily the benzyl-deprotection under the reductive condition, affording diol **50** in the quantitative yield. So, we improved our synthetic route and increased the yield of those three steps from 62.5% to 91%. The following mesylation of diol **50** led to the key intermediate **51**. As the nucleophility of the amino groups in compound **51** was reduced by the Boc-protection, an excess of NaH was needed for cyclisation. The obtained heterocycle **52** was easily separable and purified, furthermore, no cross-cyclisation product analogous to that of **25a** was observed (obviously because of the steric reasons). Deprotection of **52** with the trifluoroacetic acid gave the corresponding salt **53**, which was converted into target compound **25** under basic conditions in 20% yield from compound **38**.



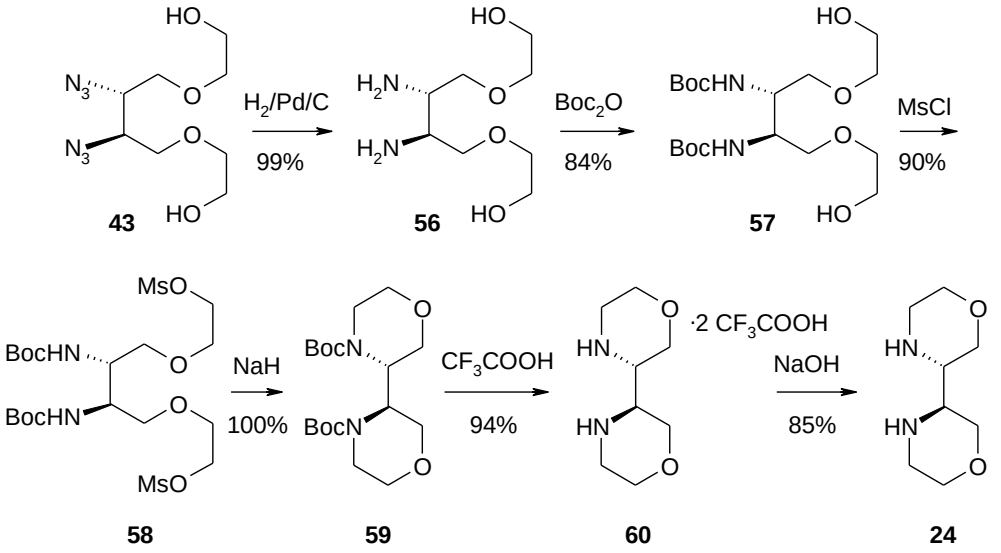
Scheme 31. Synthesis of bimorpholine **25**

In addition to the four possibilities discussed above (Scheme 27), we also attempted to synthesise bimopholine **25** via the corresponding lactam, which forms by the reductive cyclisation of azido ester. Unfortunately, the reduction of azide functionality in ester **44** (the synthesis of **44** is outlined in Scheme 26) led to a mixture of six- and seven-membered ring compounds **54** and **55** in approximately 1:1 ratio (Scheme 32).



Scheme 32. Synthetic route via lactam

The synthesis of bimorpholine **24** followed the analogous general scheme as for bimorpholine **25** (Article II). The catalytic hydrogenation of the azido groups afforded diamino diol **56** (Scheme 33). The following standard transformations (protection with Boc_2O and mesylation) led to the key intermediate **58** in high yield. Similarly to the cyclisation step for bimorpholine **25,** the ring-closure reaction was also effective and the protected bimorpholine **59** was obtained in 100% yield. Deprotection of the amino groups with trifluoroacetic acid gave the corresponding salt **60**, which was isolated under basic conditions as a free amine - bimorpholine **24** - in good yield (65% from **43**).



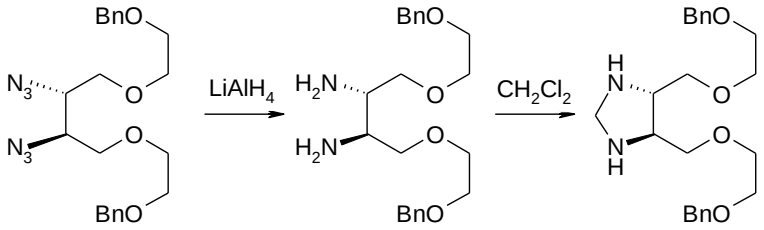
Scheme 33. Synthesis of bimorpholine **24**

In conclusion, our synthetic route is suitable to obtain bimorpholines **24** and **25** without the formation of the cross-cyclisation product during the ring-closure. The cyclisation-yields are high for both bimorpholines, 100% for **24** and 99% for **25**. The entire synthetic route is quite simple as it contains basic functional groups (or protective group) transformations. The overall yield of compounds **24** and **25** for the multistep procedure from compound **26** was 26% and 15%, respectively. The elaborated synthetic route allows preparing both enantiomers of 2,2´- and 3,3´-bimorpholine.

6. 4. Formation of aminalic side-products

The synthesis of bimorpholine **24** led to some interesting side-products, which are outlined here.

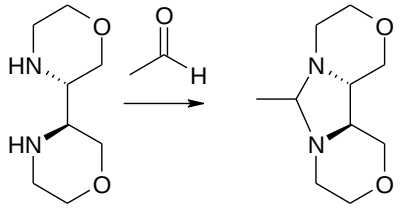
Our initial attempts to reduce the azide function and cleave of benzyl-protection in an one-step procedure surprisingly resulted in an aminalic product. We tried to realise this goal by treatment of diazide **42** with $LiAlH_4$ (Scheme 34). The reduction of azido groups occurred very fast, but as it is known, in the presence of an amine, benzyl group does not cleave [48]. However, the further purification of crude amine **61** gave aminal **62**. The obtained amine was so reactive that extractive work-up with CH_2Cl_2, followed by flash chromatography in slightly acidic conditions, led to the corresponding aminal **62**.



42 **61** **62**

Scheme 34. Formation of aminal **62**

The work-up procedure in the final step of preparation of bimorpholine **24** also led to an analogous result. Triturating compound **24** with Et_2O afforded aminal **63** (Scheme 35). NMR analysis of Et_2O used showed the content of acetaldehyde (~0.1%) that makes the formation of the corresponding aminal possible.

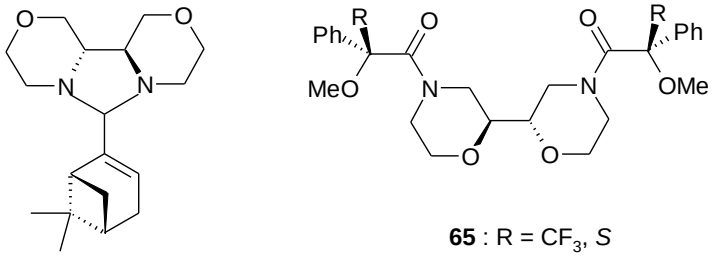


24 **63**

Scheme 35. Formation of aminal **63**

6. 5. Determination of the enantiomeric purity of bimorpholines (Article II)

To determine the enantiomeric purity of our bimorpholines, different derivatisation methods were used. Bimorpholine **24** as 1,2-diamine was converted into diastereomeric aminal derivative **64** with (1*R*)-(-)-myrtenal and bimorpholine **25**, which as 1,4-diamine can not give the corresponding aminal derivative, was derivatised into diastereomeric amides **65** and **66** with (*S*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid and (*R*)-(-)-α-methoxyphenylacetic acid (Figure 1).



64

65 : R = CF_3, *S*

66 : R = H, *R*

Figure 1. Diastereomeric derivatives of bimorpholine **24** and **25**

The NMR analysis showed that the enantiomeric excess of both bimorpholine **24** and **25** is very high (*ee* >98%).

Summary

The goals of the present work to construct an appropriately substituted intermediate containing *N*- and *O*-functionalities and to find a method for ring-closure process were realised. The elaborated synthetic route is quite simple and allows bimorpholines **24** and **25** to be obtained without formation of the cross-cyclisation product during the ring-closure.

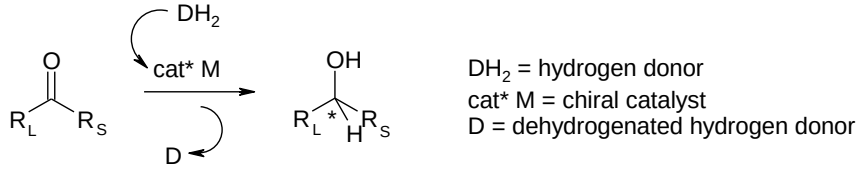
The results obtained will be valuable for designing substituted 2,2′- and 3,3′-bimorpholines. These studies can also be of interest for the synthesis of other analogous types of chiral ligands having a C_2-symmetric nature.

The synthesised chiral heterocyclic compounds with the C_2-symmetric character can be used as ligands or auxiliaries in many asymmetric transformations. The heterocyclic-bridged structure of the bimorpholines obtained can result in conformationally restricted chelation with metals, which leads to high stereodifferention.

7. Part II

ASYMMETRIC TRANSFER HYDROGENATION OF KETONES

The reduction of multiple bonds by help of a hydrogen donor in the presence of a catalyst is known as hydrogen transfer reduction or transfer hydrogenation [50].



Scheme 36. General scheme of asymmetric transfer hydrogenation of ketones

The asymmetric transfer hydrogenation of ketones is an ideal way for synthesis of chiral secondary alcohols in view of the operational simplicity, environmental friendliness and economics. This reaction employs hydrogen donors in place of hydrogen gas and is promoted by a transition metal complex coupled with an inorganic base [51]. This method avoids the risks associated with handling of molecular hydrogen and also the necessity of high-pressure equipment. The most widely used hydrogen donors are 2-propanol (generally used with sodium or potassium hydroxide as base) or formic acid (generally used with triethylamine). It has been discovered that the use of catalytic amount of base in the metal catalysed transfer hydrogenation of ketones by 2-propanol dramatically increases the activity of the catalyst [52].

7. 1. Mechanism of the asymmetric transfer hydrogenation of ketones

From the mechanistic point of view, two general reaction paths have been described for the transfer hydrogenation of ketones: 1) direct hydrogen transfer – a concerted process, and 2) hydridic route – a stepwise process [53].

The direct hydrogen transfer process involves a six-membered cyclic transition state in which both the hydrogen donor (*i*-PrOH) and hydrogen acceptor (ketone) are held together in

close proximity to the metal centre (Figure 2). This cyclic transition state is similar to that proposed for the Meerwein-Ponndorf-Verley reduction [54].

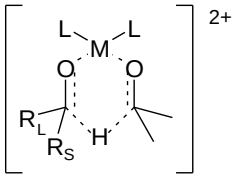
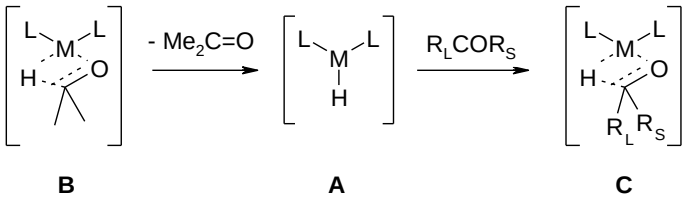


Figure 2. Six-membered cyclic transition state of direct hydrogen transfer

Hydridic route proceeds in a stepwise way via metal hydride species **A**. They are formed from complex **B** derived from the catalyst and the hydrogen donor, followed by the elimination of acetone. Then the hydride transfer step from the metal to substrate **C** follows (Scheme 37).



Scheme 37. Hydridic route of the transfer hydrogenation of ketones

The exact mechanism of the process depends on the metal catalyst and hydrogen donor. The main group elements are reported to undergo a direct hydrogen transfer route preferentially. Historically, metal alkoxides (typically aluminium 2-propoxide) have been used as stoichiometric reagents for that purpose. Recently, certain lanthanide complexes have proved to act as excellent catalysts [55]. Transition metal complexes, in contrast, react in the hydride mechanism. Those metal hydride species have been reported in various systems [56,57,58,59].

7. 2. Heteroatom-containing ligands for the asymmetric transfer hydrogenation of ketones

Many heteroatom-containing ligands have been successfully employed for the asymmetric transfer hydrogenation of ketones, most commonly together with rhodium, ruthenium or iridium metal-complexes [53].

Historically, phosphorus compounds were the first type of ligands used in hydride transfer reduction [60]. In general, the conversion and enantioselectivity were modest and, in some cases, the use of harsh conditions was required. In contrast, for asymmetric hydrogenation of functionalised ketones, the BINAP-Ru dihalide complexes have been used successfully [61]. However, for the hydrogenation of simple ketones and of α-diketones, this system was not efficient. A breakthrough in that process was provided by the invention of chiral Ru diphosphine-diamine mixed-ligand complexes (Figure 3) [62].

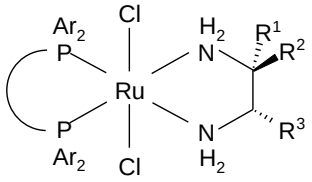


Figure 3. Chiral Ru diphosphine-diamine mixed-ligand complex

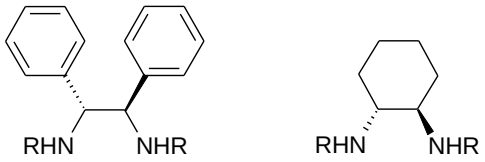
In fact, none of catalysts can be universal because of the structural difference of ketones. To obtain a high enantioselectivity, a right catalyst as well as the appropriate reaction conditions must be selected. In this respect, the mixed-ligand system has a necessary flexibility: a wide range of chiral catalysts can be prepared by combinations of chiral diphosphines and diamines [63,64,65,66].

Additional introduction of the nitrogen atom into the ligand-structure increased the potential of this type of chiral ligands in the transfer hydrogenation. In fact, until 1981 the observed enantioselectivities were quite low (up to 20%). Using a new catalyst since 1991, the obtained enantioselectivities by asymmetric transfer hydrogenation have improved to the same level as reached in the asymmetric hydrogenation [50]. Differently from the asymmetric hydrogenation, in the asymmetric transfer hydrogenation, the most widely used chiral ligands are nitrogen-donors and not phosphorus-donors.

In the literature survey presented below, the asymmetric transfer hydrogenation reactions are classified according to the nature of chiral *N*-ligand used in the complex of metal catalyst. The influence of chiral ligands, metal precursors, basic co-catalysts and substrates are discussed. When possible, the chiral complexes are characterised and the suggested catalytic cycles are presented.

7. 2. 1. Diamine and diimine ligands

Lemaire and co-workers have investigated Rh-complexes of various C_2-symmetric chiral diamines **67**-**68** (Figure 4) as viable catalysts for the transfer hydrogenation of prochiral ketones [67,68].



67

a: R = H,
b: R = Me,
c: R = *i*Pr

68

a: R = H,
b: R = Me

Figure 4. C_2-symmetric chiral diamines

The obtained enantioselectivities were modest, the best result was obtained using methyl-substituted secondary diamine **67b** with $[Rh(hd)Cl]_2$ (*ee* 67% for the reduction of acetophenone, substrate/Rh/L*/KOH = 20/1/2/6 molar ratio where Rh = $[Rh(hd)Cl]_2$ dimer with two Rh atoms, at the room temperature). The use of analogous primary diamine **67a**

under the same conditions decreased the enantioselectivity (to *ee* 17%); probably due to the less basic and less sterically demanding nature of primary amine than substituted amine ligands. It is noteworthy that cyclohexyldiamine ligands **68** induced very low enantioselectivity or even the lack of selectivity (with primary diamine **68a** 12% *ee*). This fact could be explained by the flexibility of the cyclohexyl part, giving the less stereodefined structure of the active Rh-complexes.

The effect of the chiral catalyst and base concentration was studied using the reduction of acetophenone as a model reaction. The activity of the catalyst was clearly dependent on its concentration (the use 0.1 mol% of catalyst gave only 2.5% conversion *vs* 1 mol% of catalyst - 100% conversion), but the stereoselectivity was not notably affected by this parameter. The increase of the KOH concentration led to the higher yield but there appeared an optimum in enantioselectivity (optimum KOH/Rh ratio equal to 6, an excess of KOH led to a drop in the selectivity: KOH/Rh = 6 - 66% *ee* versus KOH/Rh = 100 - 52% *ee*).

Lemaire has published the results of the studies on the nature of the Rh-diamine complexes in the asymmetric hydride transfer reduction of carbonyl compounds [69]. They combined the result of a theoretical and an experimental study. The theoretical results referred to the possibility of an active complex, which includes a diene and a diamine. To confirm or reject these assumptions, they tried to synthesise and isolate different complexes with one or two diamine ligands. Different amounts of diamine (1, 2 or 10 equiv.) were used, but elemental analyses showed that in all cases only one diamine and one cyclooctadiene were coordinated to the rhodium atom (Figure 5).

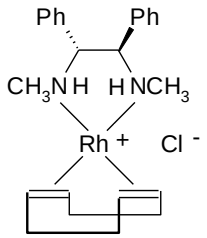
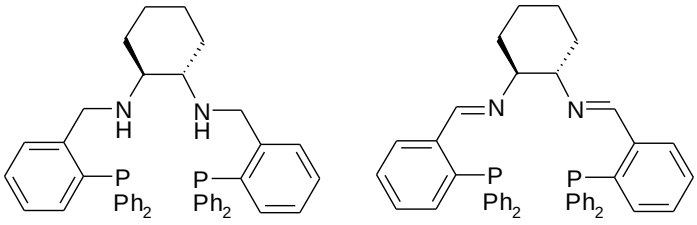


Figure 5. Rh-diamine complex from $[Rh(cod)Cl]_2$ and diamine **67b**

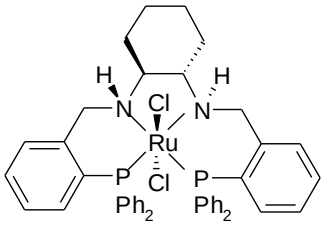
Testing the Rh-precursors with different diene ligands under the same conditions showed that hexadiene gave a higher *ee* (55%) than cyclooctadiene (47%), however, with lower conversion values. When ethylene was used, 51% *ee* was obtained, but conversion remained very low (<10%). The nature of the metallic precursor influenced both factors: activity and selectivity of the reduction, which suggests that the diene is coordinated to the metal in the active complex.

Noyory has described the use of analogous tetradentate *P*,*N*-ligands. C_2-symmetric diphosphine/diamine and diphosphine/diimine ligands **69** and **70** (Figure 6) were used in the transfer hydrogenation of aromatic ketones [70]. The chiral catalysts from *trans*-$RuCl_2(DMSO)_4$ and ligand **69** or **70** (in equimolar ratio) were synthesised. These crystal complexes are stable to air and moisture at the room temperature. X-ray analysis of Ru-**69** and Ru-**70** complexes indicates to a distorted-octahedral geometry that approximates to C_2-symmetry, where the ligand **69** or **70** occupies the four equatorial coordination sites and two chloro ligands are in the axial position. In the Ru-**69** complex, the nitrogen atoms become stereogenic (Figure 6).

The two ligands react very differently, depending on the type of nitrogen atoms. In the Ru-catalysed reduction of acetophenone, diimino ligand **70** was almost inactive whereas structurally similar diamino ligand **69** gave the corresponding alcohol with 97% *ee* in 93% yield (substrate/Ru-**69**/*i*-PrOK = 200/1/0.5, at 45 °C). This fact indicates that the presence of the NH functions is important for the high reactivity of the *P,N*-based catalyst.



69 **70**

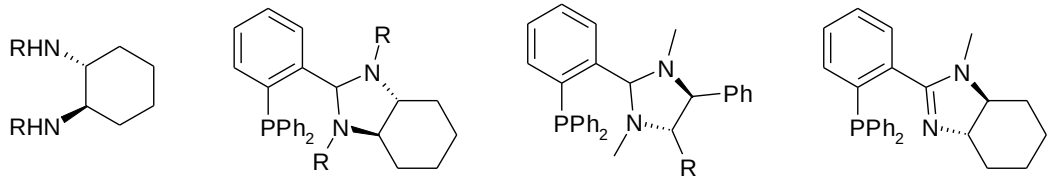


Ru-**69**

Figure 6. C_2-symmetric diphosphine/diamine and diphosphine/diimine ligands

The rate and stereoselectivity were slightly influenced by the reaction conditions. The use of a small amount of potassium 2-propoxide (0.5 equiv to Ru) gave an optimal result. An increase of the base/Ru ratio from 0.5:1 to 2:1 slightly accelerated the reaction, but led also to a slight loss of enantioselectivity. The reduction of acetophenone at the room temperature gave the same result (97% *ee*) as at 45 °C, but the reaction time increased from 7 h to 25 h.

Recently, Kim has reported the use of *N,N′*-dialkylated diamine derivatives with $RuCl_2(PPh_3)_3$ in the asymmetric transfer hydrogenation of aromatic ketones [71]. They studied the influence of secondary diamines **68** and chiral phosphinoimidazolidines **71**, **72** and phosphinoimidazoline **73** (derived from the corresponding diamines) on the hydride transfer reduction of ketones (Figure 7).



68 **71** **72** **73**

a: R = Me,
b: R = Et,
c: R = Bn

a: R = Me,
b: R = Ph

Figure 7. Chiral diamine, phosphinoimidazolidine and -imidazoline ligands

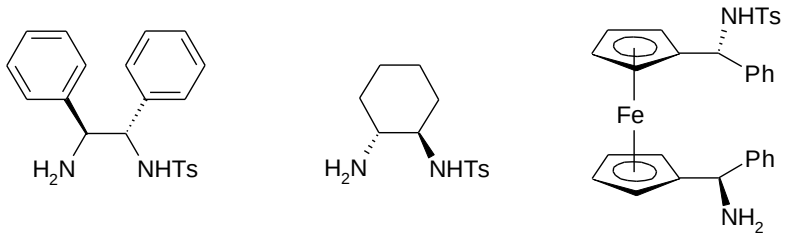
The reactions with chiral Ru-catalysts, promoted by NaOH, proceeded with remarkable reactivity and selectivity (substrate/Ru/L* = 50/1/1.5, at 82 °C). The use of *N*-methylated

diamine **68** gave the corresponding alcohols up to 71% *ee* (56% *ee* in >99% conversion for the reduction of acetophenone). The new ligands **71**, **72** and **73** were very efficient (up to 93% *ee* and in the most cases >99% conversion), the enantioselectivity and the reactivity were strongly dependent on the structure of ligands. The imidazolidine **71a** of *N*-methylated diamine derivative, which were sterically less hindered at the nitrogen atom, gave much better enantioselectivity than those of *N*-benzylated diamine derivative **71c** (89% *ee* versus 75% *ee* for the reduction of propiophenone).

The influence of the pre-formation of the complex on the reactivity was also investigated. The preformed catalyst was about 20 times faster than that prepared *in situ*. The variation of Ru-precursor and base source influenced the reactivity and stereoselectivity. The use of sodium isopropoxide instead of sodium hydroxide improved the reactivity (3 times faster), while the enantioselectivity was independent of the kind of base (the concentration of the base is unknown). Comparison of Ru-precursors showed that with $RuCl_2(PPh_3)_3$, slightly higher enantioselectivities were obtained than when by help of $[RuCl_2(p\text{-cymene})]_2$ (67% *ee* versus 53% *ee* for the reduction of propiophenone).

7. 2. 2. *N*-monotosylated diamine ligands

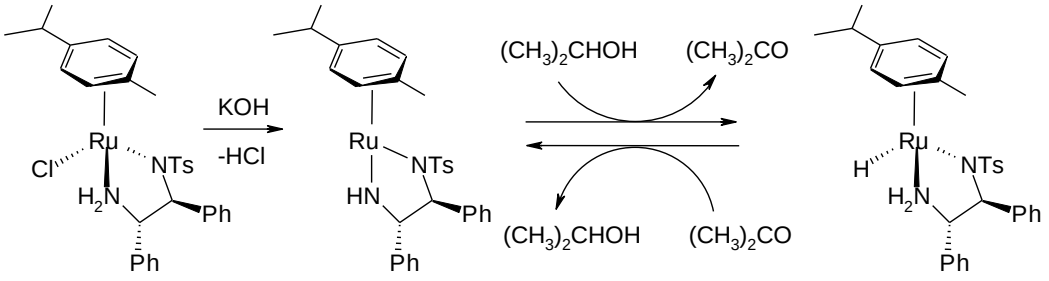
Modification of the basic structure of primary diamine **67** led to the most selective ligand ever reported for the hydride transfer reduction – *N*-monotosylated diamine **74** (Figure 8), described by Noyori [72]. The reduction of acetophenone with 2-propanol as a hydride source and using ligand **74** with $[RuCl_2(mesitylene)]_2$ gave 97% *ee* in 95% yield (substrate/Ru/L*/KOH = 400/1/4/10 molar ratio where Ru = $[RuCl_2(mesitylene)]_2$, at the room temperature). The use of the Ru/L* molar ratio 1/4 allows to chelate two chiral *N*-ligands per one Ru atom where one chiral *N*-ligand replaces the arene-ligand. If the catalyst contains only one chiral *N*-ligand, an excess of the ligand will be present in the reaction mixture.



74 **75** **76**

Figure 8. *N*-monotosylated diamines

Later kinetic studies and X-ray analysis of the chiral Ru-arene complex (both showed the monomeric structure) revealed that the metal is coordinated to one *N*-monotosylated diamine ligand and to an arene unit. To prepare the chiral catalyst, it is sufficient to use the molar ratio of Ru/L*/KOH = 1/2/2. The key intermediate was the metal hydride complex instead of the alkoxide derivative [57] (Scheme 38). The experimental studies showed that complex **74b**, forming by treatment of **74a** with base, transformed into a stable ruthenium hydride complex **74c** as a single diastereomer.



Scheme 38. Formation of the active metal hydride complex

Both **74b** and **74c** were able to catalyse the transfer hydrogenation of ketones in the absence of the base. The base was necessary only for the generation of the "true" catalyst **74b**.

Noyori postulated that hydrogen transfer occurs via a six-membered cyclic state (Figure 9), which is stabilised by hydrogen bonding from the NH to the carbonyl oxygen [73].

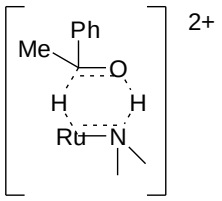


Figure 9. A postulated six-membered cyclic state for hydrogen transfer

Knochel has reported the chiral monotosylated ligands **75** and **76** (Figure 8), derived from diaminocyclohexane and diaminoferrocene [74]. The counterpart of ligand **74**, *N*-monotosylated diamine **75** with $[RuCl_2(p\text{-cymene})]_2$ gave 89% *ee* in 97% conversion for the transfer hydrogenation of acetophenone (substrate/Ru/L*/KOH = 200/1/4/10, at 22 °C). The use of **76** led to significantly poorer results (56% *ee* for the reduction of acetophenone).

Also, the first asymmetric transfer hydrogenation of acetylenic ketones by help of the monotosylated ligand **74** with Ru-precatalysts and 2-propanol as the hydride source, with excellent enantioselectivities and high catalytic efficiency was described [58] (up to 98% *ee* in >99% yield, with substrate/chiral catalyst molar ratio of 100 – 200, or even 1000 in certain cases, at the room temperature). Carpentier has reported the use of the same catalytic system for the asymmetric transfer hydrogenation of functionalised ketones [75] (84% *ee* for reduction of 2-acetylpyridine).

The asymmetric transfer hydrogenation of acetophenone has also been catalysed by iridium precursor with ligand **74**, giving 92% *ee* in 87% conversion [76] (substrate/Ir*/KO*t*Bu = 20/1/4, at the room temperature).

For this type of ligands (**74**, **75** and **76**, Figure 8), also formic acid/triethylamine mixture (5:2) has been successfully employed as the hydrogen donor. Using ligand **74** with Ru-precursor in the HCOOH/Et_3N system reached 98% *ee* for acetophenone [77] (substrate/Ru/L*/Et_3N = 400/1/2/4, at 28 °C). Also, the transfer hydrogenation of imines occurred by this system with high stereoselectivity [78] (up to 97% *ee*).

Ligands **75** and **76** with $[RuCl_2(p\text{-cymene})]_2$ for the transfer hydrogenation of aromatic ketones gave even better enantioselectivity with the formic acid than 2-propanol as the

hydrogen source [74] (with Ru-**75** catalyst 94% *ee* versus 89% *ee* and Ru-**76** 83% *ee* versus 56% *ee* for the reduction of acetophenone).

7. 2. 3. Oxazoline and pyrrolidine ligands

Pfaltz et al. have reported the transfer hydrogenation of aromatic ketones catalysed by $[Ir(cod)Cl_2]_2$ with C_2-symmetric bis(oxazoline) ligands **77** (Figure 10) [79] (from 47 to 91% *ee*; 58% *ee* for reduction of acetophenone, substrate/Ir/L*/KOH = 200/1/2.6/4 where Ir = $[Ir(cod)Cl_2]_2$, at 80 °C). The exact structure of ligand **77** was important: the optimal result appeared with isopropyl-substituted oxazole rings. Recently, Gomez and Lemaire presented their studies on the catalytic behaviour of several C_2-symmetric bis(oxazoline) ligands **78**, **79** and **80** (Figure 10) for the hydride transfer reduction of acetophenone [80]. For both complexes of $[Ru(cod)Cl_2]_2$ or $[Ir(cod)Cl_2]_2$ with ligand **78**, the enantioselectivity remained low (up to 38% *ee* for the reduction of acetophenone with Ru-complex; substrate/M/L*/KO*t*Bu = 40/1/2(or 4)/8 where M = $[Ru(cod)Cl_2]_2$ or $[Ir(cod)Cl_2]_2$, at the different reaction temperature from 0 to 80 °C). The excess of ligand induced a higher activity, but the selectivity remained practically unchanged.

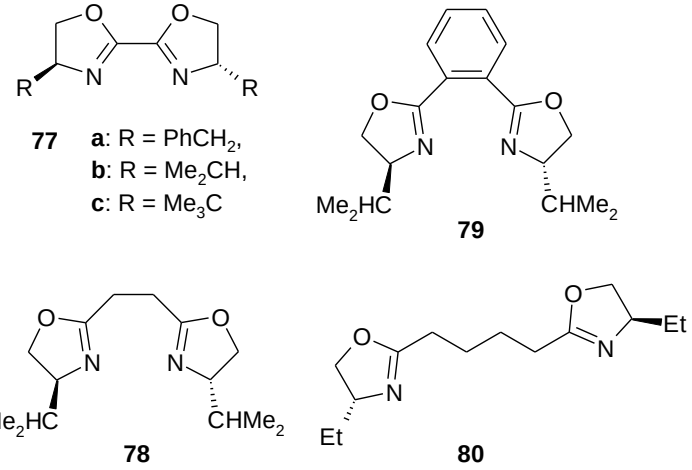
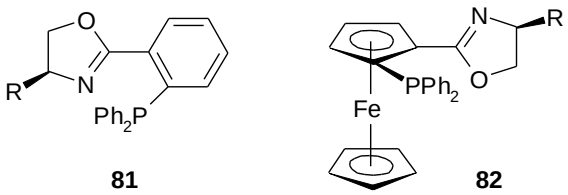


Figure 10. Chiral C_2-symmetric bis(oxazoline) ligands

Transfer hydrogenations of aromatic ketones as well as a representative dialkyl ketone by the complexes of $RuCl_2(PPh_3)_3$ and phosphinooxazolines **81** (Figure 11) were found to proceed with a high enantioselectivity [81] (up to 94% *ee* for the reduction of acetophenone, substrate/Ru/L*/NaOH = 1000/1/1.3/25, at 82 °C). The catalytic activity of chiral ferrocenyl phosphinooxazolines **82** (Figure 11) with $RuCl_2(PPh_3)_3$ was also studied in the hydride transfer reduction of aromatic ketones, leading to 94% *ee* for the reduction of acetophenone [82] (substrate/Ru/L*/KO*i*Pr = 1000/1/1.3/25, at the room temperature). The authors are convinced that an additional phoshine part (from $RuCl_2(PPh_3)_3$) to form an active complex was necessary for the reaction to proceed with high activity and selectivity. A triphenylphosphine-free catalyst prepared from ligand **82** and $RuCl_3 \cdot 3H_2O$ was less active and its use for the reduction of acetophenone gave much lower enantioselectivity than the catalyst from $RuCl_2(PPh_3)_3$ (9% *ee* versus 94% *ee*).

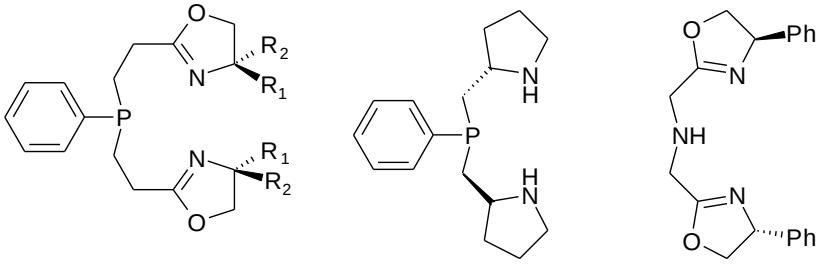


81 **82**

Figure 11. Chiral phosphinooxazoline ligands

Ligands **81** and **82** that do not bear the C_2-symmetry can form several diastereomeric complexes that could exhibit different reactivities and selectivities; therefore it is difficult to find the relationship between the structure of ligand and the activity-selectivity of the complex. Tri- and tetradentate ligands with C_2-symmetry were proposed for this purpose. These ligands form as a rule a deeper chiral pocket around the metal centre.

Zhang and co-workers have prepared and studied the influence of various tridentate *P*,*N*-containing ligands on Ru-catalysed transfer hydrogenation [83,84,85]. It has found quite recently that among them C_2-symmetric tridentate *NPN*-type ligands **83** and **84** (Figure 12) exhibit high activity and notable selectivity. The use of $(RuCl_2C_6H_6)_2$ with ligand **83** in the transfer hydrogenation resulted in even higher selectivity in the case of aliphatic ketones (up to 92% *ee*, substrate/Ru/L*/NaH = 200/1/2.2/30 where Ru = $(RuCl_2C_6H_6)_2$, at the room temperature) than of aromatic ketones (up to 79% *ee*, at 80 ^oC) [85]. The analogous bipyrrolidine ligand **84** under similar conditions (instead of NaH NaO*i*Pr was used) possessed a high activity but quite moderate stereoselectivity (up to 48% *ee*) [84].



83 **a**: R^1 = Ph, R^2 = H **84** **85**
b: R^1 = H, R^2 = *i*Pr

Figure 12. Chiral tridentate *NPN*-type ligands

Despite the crucial role of NH function (postulated by Noyori in full paper about mechanistic aspects [73]), Ru-complex with ligand **84** remained less selective than Ru-complexes with ligand **83**. The absence of substituents in the pyrrolidine ring and the length of the chain between the heteroatoms may cause this difference. A complex-pocket formed with ligand **83** was obviously deeper and sterically more hindered, so it will lead to higher stereoselectivity.

Zhang has reported the design and use of chiral bis(oxazolinylmethyl)amine ligand **85** (Figure 12) [86]. They expected that when replacing the phosphine with a secondary amino group, the obtained ligand **85** would form a six-membered cyclic transition state, which can cause a high enantioselectivity of transfer hydrogenation of ketones (Figure 13).

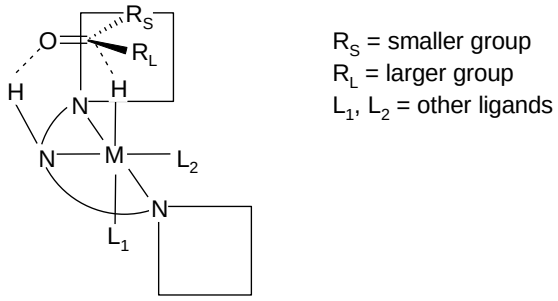


Figure 13. Schematic depiction of the cyclic transition state for transfer hydrogenation of ketones

Indeed, this chiral tridentate ligand **85** proved to be a highly efficient catalyst with $RuCl_2(PPh_3)_3$ for the transfer hydrogenation of aromatic ketones (up to 98% *ee* for the reduction of acetophenone, substrate/Ru/L*/NaO*i*Pr = 100/1/1.1/1, at 82 ºC). The best molar ratio of base/catalyst was one, the use a larger amount of the base accelerated the reaction but led to a decrease of the enantioselectivity (1 equiv of the base gave 84% *ee vs* 15 equiv of base 60% *ee*). The presence of an NH moiety in the ligand structure is important for obtaining a high activity and stereoselectivity. Replacing the NH with NCH_3 led to a significant drop in the enantioselectivity and activity (acetophenone: 10% *ee* instead of 98%; 16.5% conversion instead of 91%).

This catalytic system had one drawback: the required removal of the free triphenylphosphine ligand, which released during the complexation. The enantioselectivity of the reaction increased considerably after the removal of the free triphenylphosphine (from 84% *ee* to 97%) and also the activity of the catalyst depended on this additional procedure (increase from 67% of the conversion in 1 h to 91% in 10 min).

7. 2. 4. Comparison of relative effectiveness of *N*-containing ligands

A wide choice of the above heteroatom-containing ligands is presented in Table 1. To compare the relative effectiveness of these ligands, the reduction of acetophenone was selected as a model-process.

Table 1. Asymmetric transfer hydrogenation of acetophenone

No	L*[a]	Metallic precursor, base[b]	S/M/L*/base	Temperature, time	Yield (%)	*ee* (%)
1	**67b**[68]	$[Rh(hd)Cl]_2$, KOH	20/1/2/6	25 °C, 7 d	100	67
2	**68b**[68]	$[Rh(hd)Cl]_2$, KOH	20/1/2/6	25 °C, 5 d	100	0
3	**69**[70]	*trans*-$RuCl_2(DMSO)_4$, KO*i*Pr	200/1/1/0.5	45 °C, 7 h	93	97
4	**68b**[71]	$RuCl_2(PPh_3)_3$, NaOH	50/1/1.5/n.d.	82 °C, 3 h	>99	56
5	**71a**[71]	$RuCl_2(PPh_3)_3$, NaOH	50/1/1.5/n.d.	82 °C, 3 h	>99	81
6	**72b**[71]	$RuCl_2(PPh_3)_3$, NaOH	50/1/1.5/n.d.	82 °C, 5 h	90	48
7	**74**[72]	$[RuCl_2(mesitylene)]_2$, KOH	400/1/4/10	r.t., 15 h	95	97
8	**74**[77]	$[RuCl_2(mesitylene)]_2$ [c]	400/1/2/4 [c]	28 °C, 20 h	>99	98
9	**74**[76]	$[Ir(cod)Cl_2]_2$, KO*t*Bu	20/1/2/4	r.t., 1 d	87	92
10	**75**[74]	$[RuCl_2(p\text{-cymene})]_2$, KOH	200/1/4/10	22 °C, 1 d	97	89
11	**75**[74]	$[RuCl_2(p\text{-cymene})]_2$ [c]	200/1/4/4 [c]	30 °C, 1 d	>99	94
12	**76**[74]	$[RuCl_2(p\text{-cymene})]_2$, KOH	200/1/4/10	22 °C, 1 d	97	56
13	**77b**[79]	$[Ir(cod)Cl_2]_2$, KOH	200/1/2.6/4	80 °C, 3 h	89	58
14	**78**[80]	$[RuCl_2(p\text{-cymene})]_2$, KO*t*Bu	40/1/4/8	r.t., 20 h	88	25
15	**83a**[85]	$(RuCl_2C_6H_6)_2$, NaH	200/1/2.2/30	80 °C, 0.2 h	72	79
16	**84**[84]	$(RuCl_2C_6H_6)_2$, NaO*i*Pr	200/1/2/30	23 °C, 1 d	96	20
17	**85**[86]	$RuCl_2(PPh_3)_3$, NaO*i*Pr	100/1/1.1/1	82 °C, 0.17 h	91	97

[a] References
[b] 2-propanol is used as hydride source unless otherwise indicated
[c] Formic acid/triethylamine (5:2) is used as hydride source (S/M/L*/Et_3N molar ratio)
n.d. – not defined

Depending on the relationship between the structure of the chiral ligand and metallic precursor, different M/L* molar ratios were chosen. The monomeric metal-precursors are chelated with an equimolar amount of ligand (or a little excess – to 1.5 equiv). The dimeric metal-precursors, which contain two metal atoms, need a double amount of a ligand; in most cases, two equiv of a ligand are used but some authors have used an excess of the ligand (4 equiv). The concentration of the base varied from 0.5 to 30 equiv, every system needs its own specific amount of the base. Also, the catalytic amount of the chiral catalyst depends on its activity in the reaction (varied from 0.25 to 5 mol%).

Summary

Some highly active and enantioselective catalysts have been developed for asymmetric transfer hydrogenation of prochiral ketones. However, none of the existing catalysts can be universal, because there exists a structurally diverse array of ketonic compounds. One has to choose appropriate metallic species and chiral ligands as well as reaction conditions, depending on the substrates.

8. GOALS OF THE PRESENT STUDY

Nitrogen-containing compounds such as chiral ligands have several distinct advantages over other analogous heteroatom-containing ligands. They have a good chelating ability; interaction with metals usually gives a stable catalytic system. The natural transition metal complexes (as porphyrines) in which nitrogen acts as a ligand atom have already proven their efficiency. Depending on the type of the ligand (as amides, amines or imines), interactions with the transition metals may vary widely. In addition to the stability of those catalytic systems, they are also easily separable from the non-basic product, and are also recyclable. The inexpensive recyclability is their special advantage over the phosphine-containing ligands (it is almost impossible to recycle phosphine-containing catalysts due to their low stability toward oxidation) [3].

Nitrogen-containing compounds can be efficient chiral ligands in several homogeneous or heterogeneous asymmetric reactions. Many successful examples of catalytic asymmetric transfer hydrogenation [53] have demonstrated that they can be used with similar or even higher selectivity than those obtained with the best chiral phosphines (see literature survey Part II).

These reports prompted us to study the catalytic behaviour of the C_2-symmetric bimorpholines as chiral ligands in the asymmetric transfer hydrogenation of ketones. Asymmetric hydride transfer reduction of prochiral aromatic ketones was used as a model process because this reaction is easy to perform and requires neither high-pressure equipment nor use of hydrogen gas. The enantiomeric purity of the corresponding alcohols is also easily determined. Isopropanol was chosen for the hydride source because that reagent is most widely used together with the basic co-catalyst and chiral rhodium, ruthenium or iridium nitrogen-containing complexes.

The main goals of the study of the C_2-symmetric bimorpholines as chiral ligands in the asymmetric transfer hydrogenation of ketones were:

- to study the influence of the bimorpholinic structure on the selectivity and reactivity of the reduction
- to find the best molar ratio of the bimorpholine and the metallic precatalyst
- to investigate the effects of different metal-precursors and the basic co-catalyst
- to study the influence of the chiral catalyst concentration and the temperature on the selectivity and reactivity
- to evaluate the efficiency of the chiral catalyst on the transfer hydrogenation of different prochiral ketones

9. ASYMMETRIC TRANSFER HYDROGENATION OF KETONES Results and discussion

9. 1. Influence of the bimorpholine-ligand (Article III)

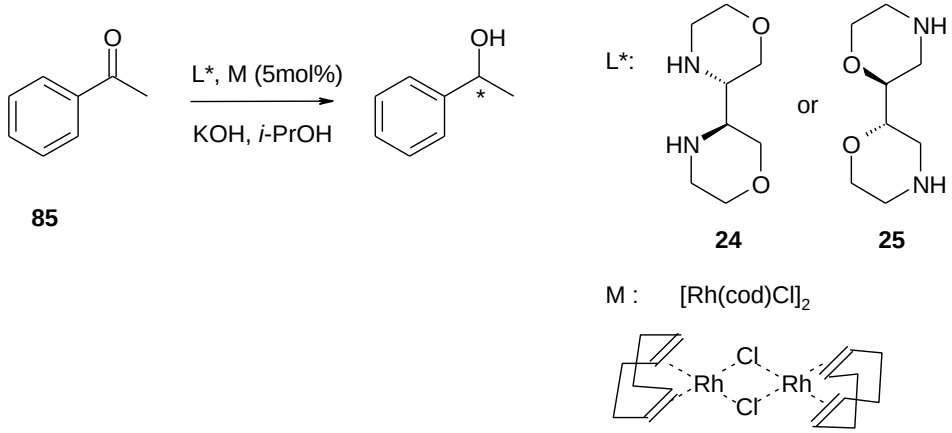
9. 1. 1. C_2-symmetric bimorpholines as chiral ligands

First, we investigated the use of $[Rh(cod)Cl]_2$ as a catalyst precursor with chiral bimorpholines **24** and **25**. The hydride transfer reduction of acetophenone **85** was selected as a model process. Lemaire et al have reported the results of the studies on the asymmetric reduction of this compound using a chiral complex (C_2-symmetric diamine and $[Rh(hd)Cl]_2$, *ee* 67%) [68].

There are contradictory data in the literature about the structure of the active complex derived from a metal-compound and a chiral bidentate diamine that participates in the catalytic reduction. Only a few X-ray structures of chiral complexes with bidentate diamine derivative ligands have been reported. Noyori has published the structure of the active species, where one *N*-monotosylated diamine **74** is bonded to the ruthenium atom together with the arene ligand [57]. According to elemental analyses and other experimental results, Lemaire has proved that the active species in the catalytic cycle are rhodium complexes with one diamine and one diene ligand [69]. Despite these results, the excess of diamine is used to stabilise the complex and to prevent the formation of black particles of rhodium, leading to the racemic product.

Bimorpholines **24** and **25** can be considered as ambidentate ligands, which may lead to the formation of dimeric complexes. Therefore, we studied the influence of the molar ratio of bimorpholines **24** or **25** and $[Rh(cod)Cl]_2$ in the catalytic complex on the enantioselectivity of the reduction of acetophenone **85** (Table 2). In a typical experiment, the catalytic complex (5 mol%) was synthesized *in situ* from bimorpholine **24** or **25**, $[Rh(cod)Cl]_2$ and KOH in *i*-PrOH by stirring the mixture at the room temperature for 1 hour prior to the addition of the substrate.

Table 2. Asymmetric reduction of acetophenone **85**[a] with Rh-bimorpholine complexes under different conditions



Entry	Molar ratio of M[b]:L*:KOH	L*	Temperature	Time	Yield[c] (%)	*ee*[d] (%)
1	1:2:6	**24**	r.t.	21 h	98	27
2	1:2:6	**24**	0 °C	7 d	77	38
3	1:4:6	**24**	r.t.	21 h	96	32
4	1:4:6	**24**	0 °C	7 d	81	34
5	1:4:6	**25**	r.t.	21 h	1.5	-
6	1:4:6	**25**	82 °C	15 h	70	0

[a] Initial concentration of substrate was 0.04-0.05M.
[b] Concentration of catalyst was 0.003-0.004M in its synthesis-step.
[c] Determined as area % by GC analyses.
[d] Determined by chiral HPLC.

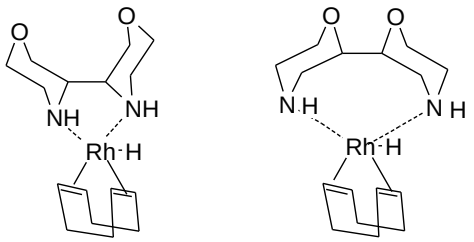
The catalyst derived from bimorpholine **24** as a ligand exhibited a high activity in the reduction. Thus, 98% conversion of acetophenone was observed at the room temperature after 21 h (Table 2, no 1). The amount of the ligand had a small effect on the enantioselectivity. As shown in Table 2, the use of four moles of the ligand instead of two moles per one mol of Rh-precatalyst caused only slightly higher *ee* value (27% vs 32%, Table 2, nos 1 and 3; $[Rh(cod)Cl]_2$ is a dimeric complex; in the Table, the molar ratio of M/L*= 1:2 corresponds to one molecule of ligand per one atom of Rh).

Decrease in the reaction temperature when the chiral Rh-complex was derived from two moles of ligand has a positive effect on the stereoselectivity. The reaction at 0 °C instead of the room temperature afforded a notable increase in enantioselectivity (*ee* 38% instead of 27%, Table 2, no 1 *vs* 2). For the chiral Rh-complex derived from four moles of ligand, a decrease in the reaction temperature has an insignificant effect on the stereoselectivity (Table 2, no 3 *vs* 4). Surprisingly enough, at 0 °C the use of two moles of ligand instead of four moles per one mol of Rh-precatalyst led to a slightly higher enantioselectivity (*ee* 38% *vs* 34%, Table 2, nos 2 and 4). At the decreased temperature, the reaction rate was, however, considerably lower and the satisfactory conversion was obtained only after 7 days (instead of 21 h).

Generally, working at low temperatures leads to an increase in the enantioselectivity of the catalytic system. However, the experimental results are quite contradictionary in this respect. This may be due to the existence of different active species in the reaction medium causing different dependence of the stereoselectivity from the temperature of reaction. In the case of the chiral Rh-complex with M/L* molar ratio 1:4, a decrease in temperature had no significant influence on the enantioselectivity of this catalytic system.

The catalyst derived from bimorpholine **25** and $[Rh(cod)Cl]_2$ had very low activity. Within typical reaction time (21 h), only 1.5% of the conversion was observed (Table 2, no 5). Thus, a higher temperature (82 ^oC) was used to perform the reaction, however, the product obtained was racemic (Table 2, no 6).

Despite structural similarity of both bimorpholines (C_2-symmetric bridged compounds with four donor sites), there is substantial difference in the geometry of the metal-chelated complexes. Bimorpholine **24** could form a five-membered ring in the metal complex (Figure 14, **Rh-24**) like a typical rhodium complex with *N*,*N*-donor ligand [69]. The complexation with bimorpholine **25** could give a less stable seven-membered ring (Figure 14, **Rh-25**) in a similar chelation. This may be the reason why only bimorpholine **24** proved to be a suitable ligand for the hydride transfer reduction of ketones.



Rh-24 **Rh-25**

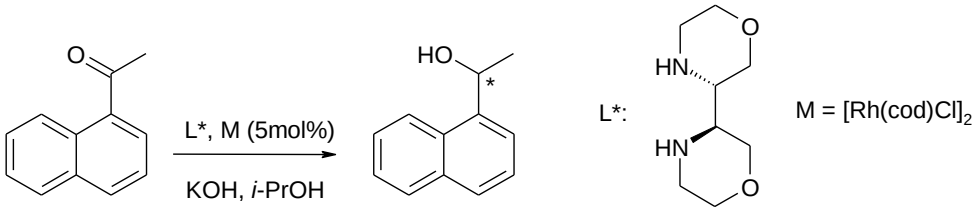
Figure 14. Possible five-membered (**Rh-24**) and seven-membered (**Rh-25**) complexes

9. 1. 2. Influence of bimorpholine 24

Bimorpholine **24** proved to be a promising ligand for the metal mediated transfer hydrogenation. Thus, the rest of studies of the asymmetric hydride transfer reduction of aromatic ketones were accomplished with bimorpholine **24**. The other factors influencing the enantioselectivity (concentration of catalyst and substrate) were studied and the optimisation of the process was carried out.

We reduced 1-acetonaphthone **86** in the similar reaction-conditions: the catalytic complex was synthesised as presented above (from bimorpholine **24**, $[Rh(cod)Cl]_2$ and KOH in *i*-PrOH at the room temperature; Table 3).

Table 3. Asymmetric reduction of 1-acetonaphthone **86** with Rh-bimorpholine **24** complex under different conditions



86 **24**

Entry	Molar ratio of M[a]:L*:KOH (conc. of cat.)	Initial concentration of substrate	Temperature	Time	Yield [b] (%)	*ee* [c] (%)
1	1:4:6 (0.004M)	0.05M	20 °C	21 h 46 h	70 83	62.5
2	1:4:6 (0.0035M)	0.05M	30 °C	21 h 46 h	83 86	63
3	1:4:6 (0.001M)	0.01M	20 °C	21 h	55	64
4	1:2:6 (0.004M)	0.05M	25 °C	4 h 21 h 46 h	54 83 86	75
5	1:2:6 (0.0037M)	0.05M	30 °C	21 h 46 h	89 92	71.5
6	1:2:6 (0.004M)	0.05M	65 °C	1 h	100	39
7	1:2:6 (0.004M)	0.05M	5 °C	21 h 70 h	63 99	51 53
8	1:2:6 (0.007M)	0.1M	25 °C	4 h 21 h	95 96	64
9	1:2:6[d] (0.0035M)	0.1M	25 °C	21 h 46 h	37 38	63

[a] Molar ratio of M/L*= 1:2 corresponds to 1 molecule of ligand per 1 atom of Rh.
[b] Determined as area % by GC analyses.
[c] Determined by chiral HPLC. The enantiomeric excess did not changed during the reaction.
[d] 1 mol% of catalytic complex was used.

The molar ratio of bimorpholine **24** and $[Rh(cod)Cl]_2$ is important in the reduction of 1-acetonaphthone **86**. Two moles of ligand per one mole of Rh-precursor gave both a better selectivity and activity than the use of four moles of ligand per one mole of Rh-precursor (Table 3, no 2 *vs* 5, *ee* increased from 63% to 71.5%, yield from 86% to 92%). In the case of the M/L* molar ratio 1:4 a change in the temperature did not have any influence on the selectivity and only a small effect on the activity (Table 3, no 1 *vs* 2). On the contrary, the selectivity and activity of the reduction with the catalytic complex derived from two equivalents of ligand clearly depends on the temperature (Table 3, no 4 *vs* 5, decrease of temperature only 5 °C led to the increase of *ee* from 71.5% to 75%). We supposed that the further lowering of the temperature would lead to an increase of stereodifferentiation. However, the decrease as well as the increase of the reaction temperature gave a lower enantioselectivity (Table 3, nos 6 and 7, at 65 °C *ee* 39% and at 5 °C *ee* 53% were obtained).

These results indicate again that the formed catalytic system obviously contains different catalytic species the activity of which has differences in temperature dependence.

We studied the effect of the concentration of the catalytic complex and of the initial concentration of the substrate on the enantioselectivity and reactivity (Table 3). The catalyst concentration in its synthesis-step varied from 0.001 to 0.007M, while the substrate/catalyst ratio remained constant (5 mol%). Thus, the real concentration of Rh-catalyst increased together with the substrate concentration. The change of concentration of the catalytic complex from 0.001 to 0.004M by help of the M/L* molar ratio 1:4 did not influence the enantioselectivity and similar results were obtained (Table 3, nos 1 and 3, *ee* 62.5% and 64%). The same effect appeared when the M/L* molar ratio was 1:2. Despite the loss in the activity, which is obviously dependent on the use 1 mol% instead of 5 mol% of catalyst, the enantioselectivity remained almost constant (Table 3, nos 8 and 9, *ee* 64% and 63%). These results indicate that the concentration of the catalyst did not influence the stereoselectivity of the reaction.

We noticed the decrease in the enantioselectivity when the substrate concentration increased (Table 3, nos 4 and 8, with 0.05M substrate concentration *ee* 75 % was obtained against 64% at 0.1M).

A reason for that could be the reverse reaction – re-oxidation of 1-(1′-naphthyl)ethanol. The obtained alcohol competes with isopropanol for being a hydride source. If one of the enantiomeric forms (e.g. the *S* form that is obtained preferentially with our catalytic complex) is oxidised faster than the other, a drop in the enantioselectivity will be observed. Also, Lemaire et al. [68] have noticed the decrease in the stereoselectivity when the substrate concentration increased and have proposed a competitive mechanism to explain that. According to these authors, a second molecule of ketone could participate in the competitive catalytic cycle (Figure 15). Obviously, the re-oxidation of 1-(1′-naphthyl)ethanol can be only a minor side-reaction.

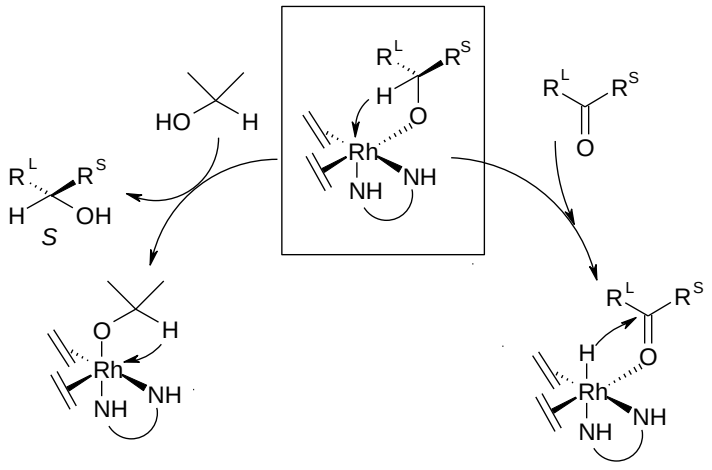
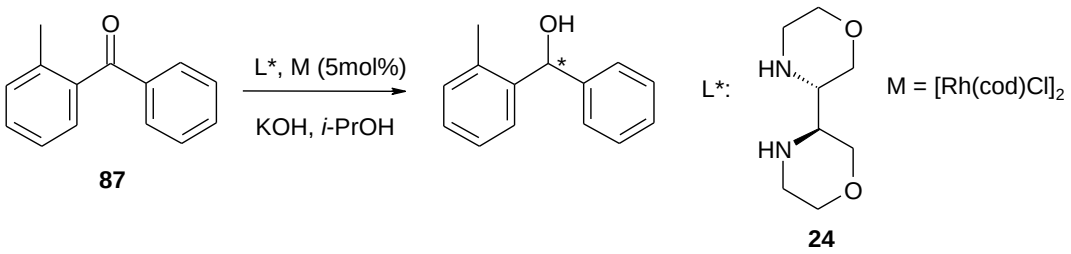


Figure 15. A proposed competitive mechanism

To study the activity of the catalyst, we changed the catalyst/substrate molar ratio. The initial concentration of the substrate was kept constant and instead of 5 mol% of catalyst, 1 mol% of it was used (Table 3, nos 8 and 9). This change caused the same stereoselectivity but a decrease in the catalyst activity: a yield from 96% to 37% dropped after 21 hours of the reaction.

We studied also the reduction of 2-methylbenzophenone **87** in the similar reaction-conditions to elucidate the influence of the amount of bimorpholine **24** in the Rh-complex on the enantioselectivity and the activity of the catalyst (Table 4). The catalytic complex was synthesised as described above (from bimorpholine **24**, $[Rh(cod)Cl]_2$ and KOH in *i*-PrOH at the room temperature).

Table 4. Asymmetric reduction of 2-methylbenzophenone **87**[a] with Rh-bimorpholine **24** complex under different conditions



87 **24**

Entry	Molar ratio of M[b]:L*:KOH	Temperature	Time	Yield [c] (%)	*ee* [d] (%)
1	1:2:6	25 °C	21 h	84	77
2	1:4:6	20 °C	46 h	33	75

[a] Initial concentration of substrate was 0.04-0.05M.
[b] $[Rh(cod)Cl]_2$ is a dimeric complex; in Table the molar ratio of M/L*= 1:2 corresponds to 1 molecule of ligand per 1 atom of Rh. Concentration of catalyst was 0.004M in its synthesis-step.
[c] Determined as area % by GC analyses.
[d] Determined by chiral HPLC.

The activity of the reduction of 2-methylbenzophenone **87** depended considerably on the amount of the ligand in the catalytic system. The M/L* molar ratio 1:2 gave the product many times faster than the M/L* molar ratio 1:4 (Table 4, nos 1 and 2, 84% yield after 21 h *vs* 33% after 46 h). With four moles of the ligand, even the elongation of reaction time did not lead to the improvement of the result.

The study of the influence of the amount of bimorpholine **24** showed that the complex derived from two moles of bimorpholine **24** and one mol $[Rh(cod)Cl]_2$ gave a higher activity than the M/L* molar ratio 1:4. The stereoselectivities of these two different catalytic systems clearly depend on the substrate. As in the reduction of acetophenone under similar conditions, a more suitable catalytic system was obtained at M/L* molar ratio 1:4 (Table 2), but for 1-acetonaphthone and 2-methylbenzophenone - the catalytic system with M/L* molar ratio 1:2 (Tables 3 and 4).

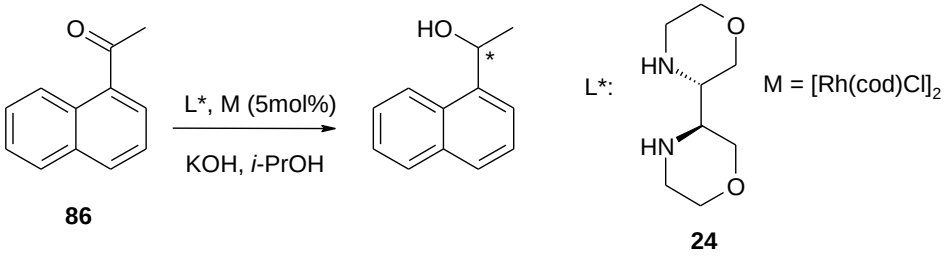
9. 2. Influence of the basic co-catalyst

It is known that the use of the catalytic amount of base activates the catalyst remarkably [52]. Lemaire et al. have shown that their catalytic system was inactive without the base [68]. They determined an optimal amount of the base at fixed M/base molar ratio 1:6.

The effect of the concentration of the basic co-catalyst was studied by help of the reduction of 1-acetonaphthone **86** (Table 5). The catalytic complex (5 mol%) was synthesised

in situ from bimorpholine **24**, $[Rh(cod)Cl]_2$ and KOH in *i*-PrOH by stirring the mixture at the room temperature for 1 hour prior to the addition of the substrate.

Table 5. Influence of the amount of the basic co-catalyst on the enantioselectivity of the reduction of 1-acetonaphthone **86**[a]



86 **24**

Entry	Molar ratio of M[b]:L*:KOH	Temperature	Time	Yield [c] (%)	*ee* [d] (%)
1	1:4:6	20 °C	21 h 46 h	70 83	62.5
2	1:4:10	20 °C	22 h	34	55
3	1:2:6	30 °C	21 h 46 h	89 92	71.5
4	1:2:3	30 °C	21 h 46 h	44 48	62

[a] Initial concentration of substrate was 0.05-0.06M.
[b] $[Rh(cod)Cl]_2$ is a dimeric complex; in Table the molar ratio of M/L*= 1:2 corresponds to 1 molecule of ligand per 1 atom of Rh. Concentration of catalyst was 0.004M in its synthesis-step.
[c] Determined as area % by GC analyses.
[d] Determined by chiral HPLC. The enantiomeric excess did not change during the reaction.

Despite the use of a different M:L* molar ratio, these four results show clearly that the increase as well as the decrease of the KOH amount had a lowering effect on the stereoselectivity. Also, the activity of the catalytic system is remarkably affected by this change. The larger amount of the base (10 equiv instead of 6) led to a drop in the enantioselectivity from 62.5% to 55% (Table 5, nos 1 and 2). The same effect was observed when a smaller KOH amount was used (Table 5, nos 3 and 4, from *ee* 71.5% to 62%). The yield of 1-(1´-naphthyl)ethanol decreased twice with the change in that parameter (Table 5, no 1 *vs* 2 and no 3 *vs* 4, from 70% yield to 34% and from 89% to 44% after the similar reaction-time, respectively).

These results can be explained by the existence of a competitive reaction. In the case of a larger amount of the base, an alcoholate (*i*-PrO^-) can form in the reaction mixture and it can compete with the diamine ligand in the complexation with the metallic precursor. The activation of the catalyst without chiral ligand leads to the formation of a racemic product. The competition between these two reactions can lead to a loss in the enantioselectivity and also in yield, if the activity of chiral metallic species is higher than those formed in the non-chiral catalyst. The use of three equivalents of the base cannot obviously generate a sufficient amount of active chiral species. It leads to a similar effect as in the case of the decrease of catalyst concentration from 5 to 1 mol% (Table 3, nos 6 and 7).

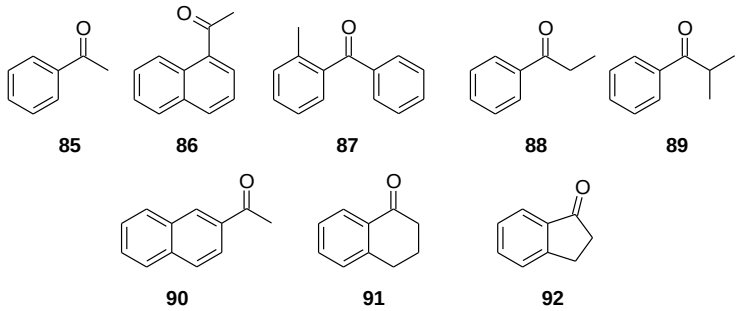
The optimal molar ratio of $[Rh(cod)Cl]_2$ to KOH in our catalytic system is 1:6.

9. 3. Asymmetric transfer hydrogenation of prochiral aromatic ketones (Article III)

According to experiments with acetophenone, the catalyst derived from bimorpholine **24** and $[Rh(cod)Cl]_2$ with the M/L* molar ratio 1:4 at the room temperature (Table 2, no 3), as the most suitable conditions for the hydride transfer reduction of aromatic ketones were found. Despite the higher enantioselectivity obtained at decreased temperature, the reaction rate was very low in these cases (Table 2, nos 2 and 4). So, room temperature was chosen, preferable for the reaction.

Ketones **85-92** were reduced under the conditions described above and the obtained results are presented in Table 6.

Table 6. Asymmetric reduction of ketones **85-92** catalysed by Rh-bimorpholine **24** complex



Entry	Ketone	Time (h)	Yield[a] (%)	*ee* (%), (*R*/*S*)[b]
1	**85**	21	96	32 (*S*)
2	**88**	46	77	40 (*S*)
3	**89**	46	55	44 (*S*)
4	**86**	46	83	63 (*S*)
5	**90**	46	82	21 (*S*)
6	**87**	46	33	75 (*S*)
7	**91**	21	61	12 (*R*)
8	**92**	46	65	3

[a] Determined as area% by GC analysis.
[b] Enantiomeric excess was determined by chiral HPLC (column: Chiralcel OD-H) and absolute configuration of the main enantiomer by comparing the optical rotation with the reference value.

As it is seen in Table 6, the highest yield was obtained in the case of acetophenone **85** (Table 6, no 1, 96% yield). The reaction was relatively fast (96% in 21 h), but the enantiomeric purity of the obtained alcohol was quite moderate (*ee* 32%). Most of other substrates required longer reaction times. Thus, propiophenone **88** was reduced to (*S*)-1-phenylpropanol in 77% yield and isobutyrophenone **89** to (*S*)-2-methyl-1-phenylpropanol in 55% yield, using the prolonged reaction time (46 h). The stereoselectivity of these reductions was low (*ee* 40% and 44% respectively, Table 6, nos 2 and 3). The hydride transfer reduction of 1- and 2-acetonaphthones **86** and **90** gave the corresponding alcohols with a satisfactorily high yield, but with considerable difference in their enantiomeric purity: the 1-acetonaphthone was reduced with higher selectivity than the 2-acetonaphthone (*ee* 63% *vs* 21%; Table 6, nos 4 and 5). The highest selectivity was observed with a "flat" substrate 2-methylbenzophenone **87** (Table 6, no 6, *ee* 75%). However,

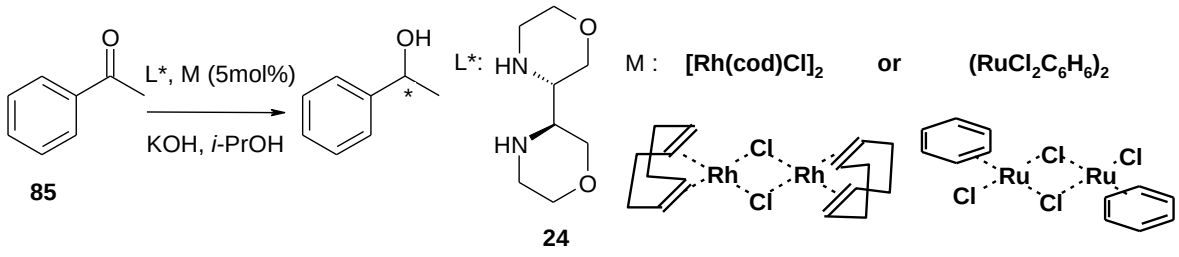
in that case the yield remained low (33%). The alicyclic substrates, 1-tetralone **91** and 1-indanone **92**, were converted to the corresponding alcohols with a satisfactory yield but with significantly lower enantioselectivity (Table 6, nos 7 and 8). The reason of the drop in the enantioselectivity may be in higher conformational flexibility of the alicyclic system than that of other used ketones.

In all cases, the selectivity of the catalytic system appeared to be forced by steric difference of the groups around the C=O bond. Branching in the alkyl chain at α-position of the carbonyl group led to higher stereoselectivity. Also, comparing 1- and 2-substituted naphthalene derivatives **86** and **90**, the sterically more hindered one with bridge at α-position affords higher reduction selectivity.

9. 4. Influence of the metal precatalyst

In this chapter we present the results of the investigation of the influence of the metallic precursor on the enantioselectivity of the reduction of acetophenone. We used another dimeric precatalyst analogous to $[Rh(cod)Cl]_2$ - $(RuCl_2C_6H_6)_2$ with bimorpholine **24** in various molar ratios. Also, the suitability of two phosphine-containing metal precursors - $RuCl_2(PPh_3)_3$ and $RhCl(PPh_3)_3$ with bimorpholine **24** was investigated. The chiral catalyst derived from the dimeric precatalyst and bimorpholine **24** was synthesised *in situ* as described above - by stirring the mixture at the room temperature for 1 hour prior to the addition of the substrate. In the case of $RuCl_2(PPh_3)_3$, the chiral catalyst was mostly prepared *in situ* by refluxing the solution [82,83]. Several experiments were made to find optimal conditions for the synthesis of this type of a catalyst. The results obtained are presented in Table 7 and 8.

Table 7. Influence of the dimeric metal precatalyst on the enantioselectivity of the reduction of acetophenone **85** [a]

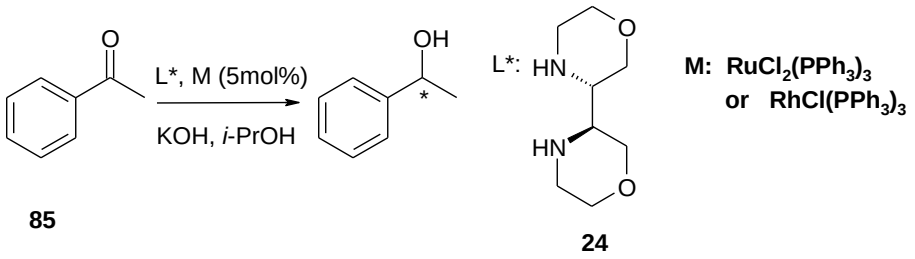


Entry	Metal precursor	Molar ratio of M[b]:L*:KOH	Temperature, Time	Yield [c] (%)	*ee* [d] (%), (*R*/*S*)
1	$[Rh(cod)Cl]_2$	1:4:6	r.t., 21 h	96	32 (*S*)
2	$[Rh(cod)Cl]_2$	1:2:6	r.t., 21 h	98	27 (*S*)
3	$(RuCl_2C_6H_6)_2$	1:4:6	r.t. 20 h, 82 °C, 5 h	- 41	 20 (*S*)
4	$(RuCl_2C_6H_6)_2$	1:2:6	r.t., 4.5 h 20 h	82 97	12 (*R*) 10

[a] Initial concentration of substrate was 0.04-0.05M.
[b] $[Rh(cod)Cl]_2$ and $(RuCl_2C_6H_6)_2$ are the dimeric complexes; in Table the molar ratio of M/L*= 1:2 corresponds to 1 molecule of ligand per 1 atom of metal. Concentration of catalyst was 0.004M in its synthesis-step.
[c] Determined as area % by GC analyses.
[d] Determined by chiral HPLC.

No reaction was detected at the room temperature when the catalytic complex was made from $(RuCl_2C_6H_6)_2$ as the transition metal source and four moles of bimorpholine **24**. When the reaction temperature was elevated up to 82 °C, the reaction proceeded in a certain extent, but the enantioselectivity of it was lower than in the analogous case with $[Rh(cod)Cl]_2$ (Table 7, no 1 *vs* 3, *ee* 20% instead of 32%). The use of M/L* molar ratio 1:2 increased the catalytic activity: reduction proceeded already at the room temperature; however, the obtained enantioselectivity was very low and it was decreased during the reaction (Table 7, no 4). The reversible hydrogen transfer between the formed alcohol and the ketone can cause a drop in the enantioselectivity. Ikariya et al. have described the rapid racemisation of chiral alcohols based on the redox properties of catalytic system [87]. Despite that poor result, one interesting factor was observed: the use of two moles of the ligand per one mol of the metallic precursor (instead of 4 moles ligand) led to the change in the absolute configuration of the product. The formed catalytic species had the opposite enantio-preference.

Table 8. Influence of the PPh_3-containing metal precatalyst on the enantioselectivity of the reduction of acetophenone **85** [a]



85 **24**

Entry	Metal precursor	Molar ratio of M[b]:L*:KOH	Temperature[c], Time	Yield [d] (%)	*ee* [e] (%), (*R*/*S*)
1	$RuCl_2(PPh_3)_3$	1:1.5:3	82 °C, 1.5 h [f]	97.5	5 (*S*)
2	$RuCl_2(PPh_3)_3$	1:1.5:3	r.t., 20 h	-	-
3	$RuCl_2(PPh_3)_3$	1:1.5:3	82 °C, 48 h	35	28.5 (*S*)
4	$RuCl_2(PPh_3)_3$	1:1.5:3 0.0025M	82 °C, 48 h	18	33 (*S*)
5	$RuCl_2(PPh_3)_3$	1:1.5:6 0.0025M	82 °C, 20 h	97	16 (*S*)
6	$RhCl(PPh_3)_3$	1:1.5:3	82 °C, 48 h	32	45 (*S*)

[a] Initial concentration of substrate was 0.04-0.05M.
[b] Concentration of catalyst was 0.004M in its synthesis-step.
[c] Catalyst was prepared by stirring at the room temperature.
[d] Determined as area % by GC analyses.
[e] Determined by chiral HPLC.
[f] Catalyst was prepared in boiling *i*-PrOH without the base.

Kim et al. [71] have reported that $RuCl_2(PPh_3)_3$ complex with chiral diamine effectively catalyses the hydride transfer reduction of aryl ketones. When we used that source of metal together with bimorpholine **24**, we found that the catalytic activity of the complex is highly dependent on its formation conditions. When preparing the complex from $RuCl_2(PPh_3)_3$ and bimorpholine **24** (the M/L* molar ratio 1:1.5 because of monomeric nature of the metal

source) in boiling *i*-PrOH without the base (the base was added together with the substrate♦), we obtained almost a racemic product (*ee* 5%; Table 8, no 1). The catalyst generated from $RuCl_2(PPh_3)_3$, bimorpholine **24** and the base at the room temperature for 1 h, was completely inactive in the reduction of acetophenone at the room temperature (Table 8, no 2). When the catalyst was prepared in the same way (r.t. 1 h) followed by the addition of the substrate and raise of temperature to reflux, the catalytic activity increased. However, the result was similar to the experiment carried out with the catalyst prepared in boiling *i*-PrOH: the reduction proceeded fast but without any stereoselectivity. When the catalyst formation-time was prolonged (not less than 3 h at r.t.) and the reaction-temperature was increased to the boiling temperature of *i*-PrOH, 1-phenylethanol was obtained in 35 % yield (Table 8, no 3). The selectivity of the catalyst remained moderate (*ee* 28.5%).

We have also studied the possible influence of the catalyst concentration on the stereoselectivity. The reaction mixture in the catalyst synthesis step was heterogeneous. Decreasing the catalyst concentration led to a small increase in the enantioselectivity (Table 8, no 4, *ee* 33%), but the conversion was very low.

To increase the activity of the catalyst, we varied the amount of the base. It is known that the use of M/base molar ratio 1:25 [81] gave a very active catalyst. Thus, we doubled the amount of the base. Unfortunately, despite the increase in the catalytic activity, this change led to a drop in the stereodifferentiation (Table 8, no 5, *ee* 16% with 97% yield after 20 h).

Changing the conditions of the catalyst formation led to clearly different catalytic systems, but all these complexes have quite poor activity and selectivity.

The first experiments with the $RhCl(PPh_3)_3$ complex showed a result similar to that obtained above: the catalyst synthesised in the boiling *i*-PrOH as well as the catalyst prepared without additional stirring-time at the room temperature gave a racemic product. There appeared a need for even prolonged catalyst formation-time at the room temperature than with the $RuCl_2(PPh_3)_3$ complex (stirring overnight instead of 3 h). The catalyst synthesised in this way worked with a moderate activity, but with surprisingly good stereoselectivity for the reduction of acetophenone (Table 8, no 6, *ee* 45% with 32% yield).

Summary

The catalytic behaviour of the C_2-symmetric bimorpholines as chiral ligands in the asymmetric transfer hydrogenation of ketones revealed that despite the structural similarities of the synthesised bimorpholines (C_2-symmetric compounds with four donor sites) an essential difference exists in the complexation with a metal. *3S,3´S*-bimorpholine **24** as a typical 1,2-diamine could form a five-membered ring in the metal complex, but *2S,2´S*-bimorpholine **25** as 1,4-diamine could give a less stable seven-membered ring in a similar chelation.

So, the best catalytic activity was obtained with $[Rh(cod)Cl]_2$ as a catalyst precursor and bimorpholine **24** as a chiral ligand. The reduction of aromatic ketones proceeds with the enantioselectivity up to 77% at the room temperature. $RhCl(PPh_3)_3$ complex as a catalyst precursor gave a very promising result. The stereoselectivity for the reduction of acetophenone was even better than with the catalyst derived from $[Rh(cod)Cl]_2$.

♦ a typical procedure for catalyst formation from $RuCl_2(PPh_3)_3$

CONCLUSIONS

The goal of the present study was to develop a synthetic route for new heterocyclic C_2-symmetric bimorpholines and to evaluate their potential use as a chiral ligand in the asymmetric catalysis.

The main results of the synthesis of C_2-symmetric bimorpholines:

- A synthetic route to obtain two new chiral bimorpholines - *3S,3´S*-bimorpholine **24** and *2S,2´S*- bimorpholine **25** was developed.
- Both bimorpholines were prepared by using the same general strategy, starting from the tartaric acid ester.
- A number of methods for synthesis of the *2S,2´S*- and *3S,3´S*-bimorpholine were developed. The optimal synthetic strategy involves three key steps:
    1. introduction of the nitrogen-containing functionality into the tartaric acid derivative;
    2. *O*-alkylation of hydroxyl groups of the obtained derivative with a functionalised C2 unit;
    3. intramolecular cyclisation.
- *2S,2´S*- and *3S,3´S*-bimorpholine were prepared in high enantiomeric purity (>99% *ee*)

The main results of the application of C_2-symmetric bimorpholines as a chiral ligand in the asymmetric transfer hydrogenation of ketones:

- *3S,3´S*-bimorpholine as 1,2-diamine proved to be a promising ligand for metal mediated transfer hydrogenation. *2S,2´S*-bimorpholine as 1,4-diamine with a precatalyst gave a less active complex without stereodirecting ability.
- The catalytic complex derived from *3S,3´S*-bimorpholine and $[Rh(cod)Cl]_2$ showed the best catalytic activity. The reduction of aromatic ketones proceeds at the room temperature with the enantioselectivity up to 77%. The optimal $[Rh(cod)Cl]_2$/base molar ratio for the catalytic system was 1:6.
- The stereoselectivity of the catalytic system depends on the structure of the substrate. The reduction of the sterically more hindered ketones afforded the higher enantioselectivity.
- The change of the $[Rh(cod)Cl]_2$ /*3S,3´S*-bimorpholine molar ratio from 1:2 to 1:4 led to different catalytic systems:
    1. The stereoselectivity in the reduction with the catalyst in M/L* molar ratio 1:2 depends on the temperature.
    2. In the reduction with the catalyst in M/L* molar ratio 1:4, the temperature has only a slight influence on the stereoselectivity.

- The catalytic complex derived from $(RuC_6H_6Cl_2)_2$ and *3S,3´S*-bimorpholine had a low stereoselectivity and the catalytic activity depends on the molar amount of the ligand. The change in the M/L* molar ratio led to the change in the enantio-preference.
- The catalyst derived from $RuCl_2(PPh_3)_3$ and *3S,3´S*-bimorpholine has a low activity and stereoselectivity. The use of $RhCl(PPh_3)_3$ with *3S,3´S*-bimorpholine led to the increase of the stereoselectivity.

REFERENCES

[1] Aitken, R. A. In *Asymmetric Synthesis*; Chapman & Hall: London, **1995**, p. 2-5.
[2] Stephenson, G. R., Genet, J.-P. In *Advanced Asymmetric Synthesis*; Chapman & Hall: London, **1996**, p. 1-8.
[3] Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159-2231.
[4] Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1-45.
[5] Bolm, C.; Chuang, T.-H.; Raabe, G. *Synth. Commun.* **1999**, *29*, 43-51.
[6] Santes, V.; Gomez, E.; Zarate, V.; Santillan, R.; Farfan, N.; Rojas-Lima, S. *Tetrahedron: Asymmetry* **2001**, *12*, 241-247.
[7] Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693-1715.
[8] Pichon, M.; Figadere, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927-964.
[9] Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1*, **1999**, 2553-2581.
[10] Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2862-2892.
[11] Oishi, T.; Hirama, M.; Sita, L. R.; Masamune, S. S*ynthesis* **1991**, 789-792.
[12] Kotsuki, H.; Kuzume, H.; Ghoda, T.; Fukuhara, M.; Ochi, M.; Oishi, T.; Hirama, M.; Shiro, M. *Tetrahedron: Asymmetry* **1995**, *6*, 2227-2236.
[13] Alexakis, A.; Tomassini, A.; Chouillet, C.; Roland, S.; Mangeney, P.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 4093-4095.
[14] Sato, M.; Sato, Y.; Yano, S.; Yoshikawa, S. *J. Chem. Soc., Dalton Trans.* **1985**, 895-898.
[15] M^{c}Coull, W.; Davis, F. A. *Synthesis*, **2000**, 1347-1365.
[16] Le Merrer, Y.; Dureault, A.; Greck, C.; Micas-Languin, D.; Gravier, C.; Depezay, J.-C. *Heterocycles*, **1987**, *25*, 541-548.
[17] Buijnsters, P. J. J. A.; van der Reijden, F. P.; Feiters, M. C.; de Gelder, R.; Sommerdijk, N. A. J. M.; Nolte, R. J. M.; Zwanenburg, B. *J. Chem. Crystallogr.* **1999**, *29*, 179-183.
[18] Kanger, T.; Ausmees, K.; Müürisepp, A.-M.; Pehk, T.; Lopp, M. *Synlett* **2003**, 1055-1057.
[19] Fitremann, J.; Dureault, A.; Depezay, J.-C. *Tetrahedron* **1995**, *51*, 9581-9594.
[20] Tanner, D.; Harden, H.; Johansson, F.; Wyatt, P.; Andersson, P. G. *Acta Chem. Scand.* **1996**, *50*, 361-368.
[21] Andersson, P. G.; Johansson, F.; Tanner, D. *Tetrahedron* **1998**, *54*, 11549-11566.
[22] Butula, I.; Karlovic, G. *Liebigs. Ann. Chem.* **1976**, 1455-1464.
[23] Denmark, S. E.; Nakajima, N,; Nicaise, O. J.-C.; Fausher, A.-M.; Edwards, J. P. *J. Org. Chem.* **1995**, *60*, 4884-4892.
[24] Desimoni, G.; Faita, G.; Mella, M. *Tetrahedron* **1996**, *52*, 13649-13654.
[25] Bolm, C.; Weickhardt, K.; Zehnder, M.; Ranff, T. *Chem. Ber.* **1991**, *124*, 1173-1180.
[26] Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1996**, *37*, 3815-3818.
[27] Davies, I. W.; Gerena, L.; Lu, N.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **1996**, *61*, 9629-9630.
[28] Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 5517-5518.
[29] Pastor, I. M.; Adolfsson, H. *Tetrahedron Lett.* **2002**, *43*, 1743-1746.
[30] Bedekar, A. V.; Andersson, P. G. *Tetrahedron Lett.* **1996**, *37*, 4073-4076.
[31] Santes, V.; Ortiz, A.; Santillan, R.; Gutierrez, A.; Farfan, N. *Synth. Commun.* **1999**, *29*, 1277-1286.
[32] McCort, I.; Ballereau, S.; Dureault, A.; Depezay, J.-C. *Tetrahedron* **2002**, *58*, 8947-8955.
[33] Stephenson, G. R. In *Advanced Asymmetric Synthesis*; Chapman & Hall: London, **1996**, p. 378-384.
[34] Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768-2771.
[35] Alvaro, J.; Grepioni, F.; Savoia, D. *J. Org. Chem.* **1997**, *62*, 4180-4182.
[36] Hirama, M.; Oishi, T.; Ito, S. *J. Chem. Soc., Chem. Commun.* **1989**, 665-666.
[37] Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297-368.
[38] Fleet, G. W. J.; Gough, M. J.; Smith, P. W. *Tetrahedron Lett.* **1984**, *25*, 1853-1856.
[39] Hirsch, J. A.; Truc, V. C. *J. Org. Chem.* **1986**, *51*, 2218-2227.
[40] Molina, P.; Vilaplana, M. J. *Synthesis* **1994**, 1197-1218.
[41] Mitsunobu, O. *Synthesis* **1981**, 1-28.
[42] Mulzer, J. In *Comprehensive Asymmetric Catalysis*; Springer: Berlin, **1999**, p. 33-97.
[43] Barnett, C. J.; Wilson, T. M.; Wendel, S. R.; Winningham, M. J.; Deeter, J. B. *J. Org. Chem.* **1994**, *59*, 7038-7045.
[44] Mao, H.; Joly, G. J.; Peeters, K.; Hoornaert, G. J.; Compernolle, F. *Tetrahedron* **2001**, *57*, 6955-6967.
[45] Bernotas, R. C.; Cube, R. V. *Tetrahedron Lett.* **1991**, *32*, 161-164.
[46] Tsunoda, T.; Ozaki, F.; Shirakata, N.; Tamaoka, Y.; Yamamoto, H.; Ito, S. *Tetrahedron Lett.* **1999**, *37*, 2463-2466.
[47] Lindström, U. M.; Somfai, P. *Synthesis* **1998**, 109-117.

[48] Greene, T. W., Wutz, P. G. In *Protective groups in Organic Synthesis*; 2th ed.; John Wiley & Sons: New York, **1991**, p. 118-143, 309-406.
[49] Scheurer, A.; Mosse, P.; Saalfrank, R. W. *Tetrahedron: Asymmetry* **1997**, *8*, 1243-1251.
[50] Zassinovich, G.; Mestroni, G. *Chem. Rev.* **1992**, *92*, 1051-1069.
[51] Ohkuma, T.; Noyori, R. In *Comprehensive Asymmetric Catalysis*; Springer: Berlin, **1999**, p. 227-246.
[52] Chowdhury, R. L.; Bäckvall, J. E. *J. Chem. Soc, Chem. Commun.* **1991**, 1063-1064.
[53] Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045-2061.
[54] March, J. In *Advanced Organic Chemistry: reactions, mechanisms, and structures;* 4th ed.; John Wiley & Sons: New York, **1992**, p. 910-918.
[55] Evans, D. A.; Nelson, S. G.; Gagne, M. R.; Muci, A. R. *J. Am. Chem. Soc.* **1993**, *115*, 9800-9801.
[56] Gladiali, S.; Pinna, L.; Delogu, G.; De Martin, S.; Zassinovich, G.; Mestroni, G. *Tetrahedron: Asymmetry* **1990**, *1*, 635-648.
[57] Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 285-288.
[58] Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738-8739.
[59] Bernard, M.; Delbecq, F.; Sautet, P.; Fache, F.; Lemaire, M. *Organometallics* **2000**, *19*, 5715-5722.
[60] Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581-1590.
[61] Noyori, R. *Angew. Chem. Int. Ed.* **2002**, *41*, 2008-2022.
[62] Noyori, R.; Ohkuma, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 40-73.
[63] Ohkuma, T.; Ooka, H.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 10417-10418.
[64] Ohkuma, T.; Ikehira, H.; Ikariya, T.; Noyori, R. *Synlett* **1997**, 467-468.
[65] Ohkuma, T.; Koizumi, M.; Muniz, K.; Hilt, G.; Kabuto, C.; Noyori, R. *J. Am. Chem. Soc.* **2002**, *124*, 6508-6509.
[66] Xie, J.-H.; Wang, L.-X.; Fu, Y.; Zhu, S.-F.; Fan, B.-M.; Duan, H.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2003**, *125*, 4404-4405.
[67] Gamez, P.; Fache, F.; Mangeney, P.; Lemaire, M. *Tetrahedron Lett.* **1993**, *34*, 6897-6898.
[68] Gamez, P.; Fache, F.; Lemaire, M. *Tetrahedron: Asymmetry* **1995**, *6*, 705-718.
[69] Bernard, M.; Guiral, V.; Delbecq, F.; Fache, F.; Sautet, P.; Lemaire, M. *J. Am. Chem. Soc.* **1998**, *120*, 1441-1446.
[70] Gao, J.-X.; Ikariya, T.; Noyory, R. *Organometallics* **1996**, *15*, 1087-1089.
[71] Kim, G.-J.; Kim, S.-H.; Chong, P.-H.; Kwon, M.-A. *Tetrahedron Letters* **2002**, *43*, 8059-8062.
[72] Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562-7563.
[73] Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.* **2001**, *66*, 7931-7944.
[74] Püntener, K.; Schwink, L.; Knochel, P. *Tetrahedron Lett.* **1996**, *37*, 8165-8168.
[75] Evereare, K.; Carpentier, J.-F.; Mortreux, A.; Bulliard, M. *Tetrahedron: Asymmetry* **1999**, *10*, 4083-4086.
[76] Halle, R.; Breheret, A.; Schulz, E.; Pinel, C.; Lemaire, M. *Tetrahedron: Asymmetry* **1997**, *8*, 2101-2108.
[77] Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521-2522.
[78] Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916-4917.
[79] Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232-240.
[80] Gomez, M.; Jansat, S.; Muller, G.; Bonnet, M. C.; Breuzard, J. A. J.; Lemaire, M. *J. Organomet. Chem.* **2002**, *659*, 186-195.
[81] Langer, T.; Helmchen, G. *Tetrahedron Lett.* **1996**, *37*, 1381-1384.
[82] Sammakia, T.; Stangeland, E. L. *J. Org. Chem.* **1997**, *62*, 6104-6105.
[83] Jiang, Q.; Van Plew, D.; Murtuza, S.; Zhang, X. *Tetrahedron Lett.* **1996**, *37*, 797-800.
[84] Jiang, Y.; Jiang, Q.; Zhu, G.; Zhang, X. *Tetrahedron Lett.* **1997**, *38*, 6565-6568.
[85] Jiang, Y.; Jiang, Q.; Zhu, G.; Zhang, X. *Tetrahedron Lett.* **1997**, *38*, 215-218.
[86] Jiang, Y.; Jiang, Q.; Zhang, X. *J. Am. Chem. Soc.* **1998**, *120*, 3817-3818.
[87] Ito, M.; Osaku, A.; Kitahara, S.; Hirakawa, M.; Ikariya, T. *Tetrahedron Lett.* **2003**, *44*, 7521-7523.

ACKNOWLEDGEMENTS

This work was conducted in the Department of Chemistry of the Faculty of Science at Tallinn Technical University.

I would like to express my sincere gratitude to all my colleagues and friends for their contribution and friendship during these years.

I wish to express my special thanks my supervisor professor Margus Lopp who encouraged me to take PhD studies and supported me in this pursuit up to the procedure of defence. I am very grateful for his inspiring ideas and interesting discussions.

Special thanks also go to my supervisor and closest colleague Tõnis Kanger for his continuous support and encouragement: for his patience all through the very busy days and for fruitful suggestions and help. Without him this work would have never been completed.

I am very thankful to Professor Tõnis Pehk for invaluable help in identifying the compounds by NMR analysis. I would like to thank Aleksander-Mati Müürisepp and Tiiu Kailas for assistance with mass spectrometry and IR analysis.

I am very grateful to my colleagues Anne Paju and Riina Aav for their help and good company during these years. Kristin Raudla, Kerti Ausmees, Marju Laars and Kärt Kulper for pleasant and stimulating atmosphere in the laboratory.

I wish also to thank my family for their love, understanding and support during my busy days.

This work was supported by the Estonian Ministry of Education, Research project No. SF035176s01 and the Estonian Science Foundation, Grants Nos. 4976 and 5628.

APPENDIX

Experimental

All reactions sensitive to the moisture or oxygen were carried out under the argon atmosphere and in the oven-dried glassware. Commercial reagents were generally used as received. All solvents were distilled prior to use. TLC analyses were performed on Merck DC-Alufolien Kieselgel 60 F_{254} silica gel plates. 40-100 μm KKC 120 silica gel was used for column chromatography. Full assignment of ^{1}H and ^{13}C chemical shifts is based on the 1D and 2D FT NMR spectra on a Bruker AMX500 instrument. Solvent peaks ($C\mathbf{H}Cl_3$ δ=7.27, $CD_2\mathbf{H}OD$ δ=3.30, $\mathbf{C}DCl_3$ δ=77.00, $\mathbf{C}D_3OD$ δ=49.00) were used as chemical shift references. The mass spectra were recorded on a Hitachi M80B spectrometer using electron ionisation (EI) at 70 eV or chemical ionisation (CI) with isobutane. IR spectra were recorded on Hitachi 270-30 infrared spectrophotometer. Optical rotations were measured using A. Krüss Optronic GmbH automatic digital polarimeter P 3002.

The conversions of the obtained alcohols were measured by capillary gas chromatography on a Shimadzu GC-14B (column 122-5022 DB-5, length 25 m, I.D. 0.25 mm, film 0.25μm). Enantiomeric excesses were determined by HPLC on a LKB 2150 system using a Chiralcel OD-H column.

Compounds **27** and **29** were synthesised followed the procedure described by Scheurer and co-workers [49].

***O*-alkylation with 2-[(methylsulfonyl)oxy]ethyl methanesulphonate 32**

To a solution of diol **30** (150 mg, 0.87 mmol) in 1,4-dioxane (2 mL) 50% NaOH aqueous solution (1 mL), Bu_4NI (80 mg, 0.21 mmol) and 2-methanesulfonyloxyethyl methanesulphonate **32** (984 mg, 4.5 mmol) were added. The reaction was stirred overnight at the room temperature and then quenched with NH_4Cl aqueous solution (3 mL) and extracted with EtOAc (3 x 10 mL). The organic extract was dried over $MgSO_4$, filtrated and the filtrate was concentrated. The crude product was purified by chromatography on silica gel (petroleum ether/EtOAc, 10:0.5 to 10:2) to afford 2,3-bis(azidomethyl)-1,4-dioxane **35** and 2,3-bis-azidomethyl-oxirane **36** in the inseparable mixture (130 mg, 86%).

Compound **35**: MS (70 eV, EI) *m/z*: 198 [M], 142, 114, 99, 86. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.27 and 3.42 (m, 4H, CH_2N_3), 3.62 (m, 2H, CHO), 3.74 and 3.84 (m, 4H, CH_2O); ^{13}C NMR (125 MHz, $CDCl_3$) δ 51.45 (CH_2N_3), 66.64 (CH_2O), 75.83 (CHO).

Compound **36**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.26 (m, 2H, CHO), 3.46 and 3.50 (m, 4H, CH_2N_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 49.42 (CH_2N_3), 53.88 ($^{1}J_{CH}$ =179 Hz, CHO).

(4*S*,5*S*)-Di-*tert*-butyl-4,5-diazidomethyl-3,6-dioxa-1,8-octanediate 44

To a solution of NaH (47 mg of a 60% dispersion in oil, 50 mg, 1.25 mmol; the oil was removed by washing with hexane 2 x 1 mL) in DMF (1.5 mL) was added diol **30** (98 mg, 0.57 mmol) in DMF (1.5 mL) at 0 °C. After the reaction subsided, bromoacetic acid *tert*-butyl ester (185 μL, 1.25 mmol) was added dropwise and the reaction mixture was

stirred at room temperature overnight. The reaction was quenched with water (10 mL), extracted with EtOAc (3 x 10 mL) and the combined organic extract was dried over $MgSO_4$. After concentration in vacuum the crude product was purified by chromatography on silica gel (petroleum ether/EtOAc, 10:1 to 10:4) affording diester **44** (94 mg, 41%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49 (s, 18H, Boc), 3.44 (dd, 2H, *J*=5.9 and 12.9 Hz, CH_2N_3), 3.73 (m, 2H, CH_2N_3), 3.78 (m, 2H, CHO), 4.13 and 4.22 (d, 4H, *J*=16.4 Hz, CH_2Boc); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.06 (Boc), 51.11 (CH_2N_3), 69.05 ($CH_2$0), 79.58 (CHO), 81.87 (Boc), 169.38 (Boc).

Decahydro-1,6-dioxa-4,9-diaza-heptalene 25a

The catalytic hydrogenation of diazidodimesylate **47** with Adams´ catalyst (Article I) led to two products in ratio 10:1, in addition to bimorpholine **25**, cross-cyclisation product **25a** was formed.

Compound **25a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.96 and 2.52, 1.99 and 2.68 (m, 4H, C**H$_2$**NH), 2.04 and 2.54, 2.05 and 2.69 (m, 4H, C**H$_2$**CH_2O), 3.38 and 3.41 (m, 2H, CHO), 3.50 and 3.82, 3.56 and 3.83 (m, 4H, CH_2O); ^{13}C NMR (125 MHz, $CDCl_3$) δ 51.15 and 54.52 (**C**H_2CH_2O), 52.54 and 55.98 (CH_2NH), 66.72 and 66.75 (CH_2O), 76.33 and 76.34 (CHO).

(2*S*,3*S*)-2,3-Bis-(2-benzyloxy-ethoxy)-1,4-butanediamine 48

To a solution of diazide **39** (1.133 g, 2.575 mmol) in MeOH (20 mL) 10% Pd/C (136 mg, 0.13 mmol) was added. The mixture was hydrogenated overnight under a hydrogen atmosphere. The catalyst was removed by filtration through Celite® and the filtrate was evaporated under vacuum affording a crude diamine **48** (996 mg, 100%). $[\alpha]_D^{21}$ –18.8 (c 1.95 MeOH). MS (70 eV, EI) *m/z*: 389 $[M+1]^+$, 359, 281, 236, 206. IR (film): 3371, 3063, 3031, 2865, 1587, 1454, 1096, 739, 699.

(2*S*,3*S*)-Di-*tert*-butyl-[2,3-bis-(2-benzyloxy-ethoxy)-1,4-butanedicarbamate 49

To a cooled solution of diamine **48** (934 mg, 2.41 mmol) in dioxane/H_2O (40 mL: 20 mL) di-*tert*-butyl dicarbonate (1.15 g, 5.30 mmol) was added at 0 ^{o}C. The reaction mixture was allowed to warm up to room temperature and an aqueous solution of KOH (2.65 mmol) was added. The reaction mixture was stirred overnight. After concentration of the reaction mixture, brine (20 mL) was added, the resulting mixture was extracted with EtOAc (4 x 50 mL) and dried over $MgSO_4$. After concentration crude product was purified by chromatography on silica gel (petroleum ether/*i*-PrOH, 10:0.25 to 10:1) affording compound **49** (1.29 g, 91%). $[\alpha]_D^{21}$ -6.1 (c 1.88 CH_2Cl_2). MS (10 eV, EI) *m/z*: 458, 415, 358, 306, 250, 91. IR (film): 3355, 2976, 2930, 2869, 1714, 1514, 1454, 1392, 1366, 1272, 1250, 1172, 1095, 738, 699.

***tert*-Butyl [2-amino-1-(5-oxomorpholin-2-yl)ethoxy]acetate 54 and *tert*-butyl {[7-(aminomethyl)-3-oxo-1,4-oxazepan-6-yl]oxy}acetate 55**

To a solution of diester **44** (90 mg, 0.255 mmol) in MeOH (2 mL) 10% Pd/C (17 mg, 0.016 mmol) was added. The mixture was hydrogenated overnight under a hydrogen

atmosphere. The catalyst was removed by filtration through Celite® and the filtrate was evaporated under vacuum affording two crude products **54** and **55** in ratio 1:1 (71 mg).
Compound **54**: ^{1}H NMR (500 MHz, DMSO) δ 1.42 (s, 9H, Boc), 2.73 and 2.86 (m, 2H, C**H**$_2$NH$_2$), 3.14 and 3.28 (m, 2H, C**H**$_2$NH), 3.55 (m, 1H, C**H**OCH$_2$NH$_2$), 3.86 (m, 1H, C**H**OCH$_2$NH), 4.00 and 4.10 (m, 2H, C**H**$_2$CONH), 4.15 (s, 2H, CH$_2$Boc), 5.2 (bs, 2H, NH$_2$), 8.04 (bs, 1H, NH); ^{13}C NMR (125 MHz, DMSO) δ 27.73 (Boc), 40.03 (CH$_2$NH$_2$), 41.26 (CH$_2$NH), 67.09 (CH$_2$CONH), 68.14 (CH$_2$Boc), 73.16 (CHOCH$_2$NH), 79.31 (CHOCH$_2$NH$_2$), 80.89 (Boc), 167.06 (CONH), 169.77 (Boc).
Compound **55**: ^{1}H NMR (500 MHz, DMSO) δ 1.43 (s, 9H, Boc), 2.77 and 2.96 (m, 2H, CH$_2$NH$_2$), 3.09 and 3.26 (m, 2H, CH$_2$NH), 3.74 (m, 1H, CHOCH$_2$NH$_2$), 3.77 (m, 1H, CHOCH$_2$NH), 3.98 and 4.04 (m, 2H, *J*=16.4 Hz, CH$_2$CONH), 4.16 and 4.17 (d, 2H, *J*=16.6 Hz, CH$_2$Boc), 5.2 (bs, 2H, NH$_2$), 8.04 (bs, 1H, NH); ^{13}C NMR (125 MHz, DMSO) δ 27.73 (Boc), 38.32 (CH$_2$NH$_2$), 41.02 (CH$_2$NH), 66.90 (CH$_2$CONH), 67.49 (CH$_2$Boc), 72.13 (CHOCH$_2$NH), 78.41 (CHOCH$_2$NH$_2$), 81.10 (Boc), 167.01 (CONH), 169.90 (Boc).

(4*S*,5*S*)-4,5-Bis-(2-benzyloxy-ethoxymethyl)-imidazolidine 62
To a solution of diazide **42** (199 mg, 0.45 mmol) in THF (5 mL) $LiAlH_4$ (86 mg, 2.27 mmol) was added under an Ar atmosphere. After stirring for 0.5 h TLC analyse showed that diazide was converted into a diamine. The reaction was quenched with THF/H_2O mixture (1.5 mL: 0.2 mL) dropwise at 10 ^{o}C. The obtained precipitate was removed by filtration and the filtrate was dried over K_2CO_3. After concentration and purification by chromatography on Al_2O_3 (CH_2Cl_2 to CH_2Cl_2: MeOH 10:0.4) afforded product **62** (82 mg, 46%). ^{1}H NMR (500 MHz, $CDCl_3$+CD_3OD) δ 3.09 (m, 2H, CHN), 3.49 (m, 4H, OC**H**$_2$CHN), 3.56 (m, 4H, CH$_2$OBn), 3.57 (m, 4H, OC**H**$_2$CH$_2$OBn), 3.70 (s, 2H, NCH$_2$N), 4.48 (s, 4H, CH$_2$Ph), 7.2-7.3 (m, 5H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$+CD_3OD) δ 59.34 (CHN), 63.38 (NCH$_2$N), 69.11 (CH$_2$OBn), 70.34 (O**C**H$_2$CH$_2$OBn), 71.30 (O**C**H$_2$CHN), 73.06 (CH$_2$Ph), 127.61 (*o*- and *p*-Ph), 128.23 (*m*-Ph), 137.69 (*s*-Ph).

Aminal 63 of bimorpholine 24 with acetaldehyde
The work-up procedure in final step of preparation of bimorpholine **24** (Article II) led to the formation of aminalic side-product **63**. Trituration of slurry (obtained after acid/base treatment) with Et_2O (content of acetaldehyde ~0.1%) several times afforded bimorpholine **24** and aminalic side-product **63** in ratio 1:4. An analytical sample was purified on the preparative TLC (CH_2Cl_2: MeOH: Et_3N 9:1:0.01) for spectroscopic analysis.
Compound **63**: MS (70 eV, EI) *m/z*: 197 $[M-1]^+$, 183, 113, 86.
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (d, 3H, *J*=5.7 Hz, CH_3), 2.45 (ddd, 1H, *J*=2.9, 9.1 and 9.8 Hz, C**H**NCH$_2$), 2.48 (ddd, 1H, *J*=3.2, 11.0 and 11.0 Hz, CH$_2$N), 2.78 (ddd, 1H, *J*=3.5, 4.8 and 11.9 Hz, CH$_2$N′), 2.81 (ddd, 1H, *J*=2.9, 9.1 and 9.8 Hz, C**H**NCH$_2$′), 2.84 (ddd, 1H, *J*=1.6, 2.8 and 11.0 Hz, CH$_2$N), 2.91 (ddd, 1H, *J*=3.5, 8.3 and 11.9 Hz, CH$_2$N′), 3.37 (dd, 1H, *J*=9.8 and 10.0 Hz, CH$_2$O), 3.50 (dd, 1H, *J*=8.0 and 11.1 Hz, CH$_2$O′), 3.55

(q, 1H, *J*=5.7 Hz, CHN(N)), 3.57 (ddd, 1H, *J*=2.8, 11.0 and 11.0 Hz, C**H**$_2$CH$_2$N), 3.67 (ddd, 1H, *J*=3.5, 8.3 and 11.0 Hz, C**H**$_2$CH$_2$N′), 3.80 (ddd, 1H, *J*=3.5, 4.8 and 11.0 Hz, C**H**$_2$CH$_2$N′), 3.81 (dd, 1H, *J*=3.5 and 11.1 Hz, CH$_2$O′), 3.85 (ddd, 1H, *J*=1.6, 3.2 and 11.0 Hz, C**H**$_2$CH$_2$N), 3.86 (dd, 1H, *J*=2.9 and 10.0 Hz, CH$_2$O); ^{13}C NMR (125 MHz, CDCl$_3$) δ 17.18 (CH$_3$), 45.65 (CH$_2$N′), 48.70 (CH$_2$N), 57.98 (**C**HNCH$_2$′), 61.69 (**C**HNCH$_2$), 65.61 (**C**H$_2$CH$_2$N′), 66.49 (**C**H$_2$CH$_2$N), 66.72 (CH$_2$O′), 69.03 (CH$_2$O), 77.69 (CHN(N)).

General procedure for the reduction of acetophenone with RuCl$_2$(PPh$_3$)$_3$ or RhCl(PPh$_3$)$_3$

A solution of bimorpholine **24** (0.015 mmol, 7.5 mol%), RuCl$_2$(PPh$_3$)$_3$ or RhCl(PPh$_3$)$_3$ (0.010 mmol, 5 mol%) and KOH (0.030 mmol, 30 mol%, 0.1 M in *i*-PrOH) in dry degassed *i*-PrOH (2.5 mL) was stirred for 20 h under Ar atmosphere. A solution of acetophenone (0.20 mmol) in *i*-PrOH (1.5 mL) was added and the reaction mixture was stirred at 82 ^{o}C for appropriate time. The reaction was monitored by TLC. After completion of the reaction, Et$_2$O (40 mL) was added and the catalyst was removed by filtration through a pad of Celite®. The filtrate was concentrated in vacuum to give the crude product, which was purified by flash chromatography on silica gel. The conversions of the corresponding alcohol were measured by capillary gas chromatography and the enantiomeric excesses were determined by HPLC using a Chiralcel OD-H column.

Curriculum Vitae

KADRI KRIIS

Date and place of birth:	March 27, 1962, Tallinn, Estonia
Citizenship:	Estonian
Family status:	Married, two children
Address:	Department of Chemistry, Tallinn University of Technology, Akadeemia tee 15, Tallinn 12618, Estonia

Education

1980−1985	University of Tartu, graduated as organic chemist
1997−1999	Tallinn University of Technology, M. Sc. degree
since 1999	Tallinn University of Technology, Ph. D. graduate student

Employment

1985−1996	Institute of Chemistry, Engineer of technology
since 1996	Institute of Chemistry, Researcher

Scientific work

Main topics of research:	asymmetric synthesis, synthesis of bioactive compounds

Curriculum Vitae

KADRI KRIIS

Sünniaeg ja -koht:	27. märts, 1962, Tallinn, Eesti
Kodakondsus:	Eesti
Perekonnaseis:	abielus, kaks last
Aadress:	keemiainstituut, Tallinna Tehnikaülikool, Akadeemia tee 15, Tallinn 12618, Eesti

Hariduskäik

1980−1985	Tartu Riiklik Ülikool, orgaanilise keemia eriala
1997−1999	Tallinna Tehnikaülikool, loodusteaduste magistri kraad
alates 1999	Tallinna Tehnikaülikool, doktorant

Teenistuskäik

1985−1996	Keemia Instituut, tehnoloogia insener
alates 1996	Keemia Instituut, teadur

Teadustegevus

Peamised töösuunad:	asümmeetriline süntees, bioaktiivsete ühendite süntees