

Stereoselective synthesis and application of bi- and trifunctional monoterpene-based compounds

PhD Thesis
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Contents

1. Introduction and aims	3
2. Literature survey	5
2.1 Synthesis and importance of chiral alicyclic 1,3-aminoalcohols	5
2.1.1 Synthetic strategies	5
2.1.2 Chemical importance – chiral auxiliaries and catalysts	6
2.1.3 Pharmacological importance	7
2.2 Synthesis and importance of chiral 3-amino-1,2-diols	8
2.2.1 Synthetic strategies	8
2.2.2 Application of chiral 3-amino-1,2-diols	12
2.2.3 Pharmacological importance of chiral 3-amino-1,2-diols	16
2.3 Synthesis and pharmacological importance of chiral diaminoalcohols	19
2.3.1 Synthetic strategies	19
2.3.2 Pharmacological importance	21
2.3.3 Application of diaminoalcohols	22
3. Results and discussion	23
3.1 Synthesis of pinane-based 1,3-aminoalcohols and diols	23
3.1.1 Synthesis of 1,3-aminoalcohols derived from (-)- β -pinene	23
3.1.2 Synthesis of diols derived from (-)- β -pinene	24
3.1.3 Partial <i>N</i> -debenzylation by flow chemistry	26
3.2 Synthesis of 3-amino-1,2-diols and <i>O,N</i> -heterocycles derived from pulegone	27
3.2.1 Synthesis of chiral 3-amino-1,2-diols	27
3.2.2 Study on the regioselectivity of the ring closure process of pulegone-based aminodiols	30
3.3 Synthesis of diaminoalcohols derived from (1 <i>R</i>)-(-)-myrtenol	32
4. Application of monoterpene-based chiral catalysts in the nucleophilic addition of diethylzinc to benzaldehyde	37
4.1 Application of pinane-based 1,3-aminoalcohols and their derivatives in the model reaction	37
4.2 Application of aminodiols derived from pulegone in the model reaction	39
4.3 Application of <i>O,N</i> -heterocycles derived from pulegone in the model reaction	40
4.4 Application of pinane-based diaminoalcohols and oxazolidinones in the model reaction	41
5. Summary	43
6. References	45
7. Acknowledgements	50

List of abbreviations

Bn: benzyl
Boc: *tert*-butoxycarbonyl
Cbz: carboxybenzyl
DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene
DCC: *N,N'*-dicyclohexylcarbodiimide
DCM: dichloromethane
DFT calculation: density functional theory calculation
DMAP: 4-dimethylaminopyridine
Ee: enantiomeric excess
IPA: isopropanol
LDA: lithium diisopropylamide
MCPBA: *m*-chloroperbenzoic acid
NMO: *N*-methylmorpholine *N*-oxide
Rt.: room temperature
TBAB: tetrabutylammonium bromide
TEA: triethylamine
TEMPO: 2,2,6,6-tetramethylpiperidinyloxy
TFA: trifluoroacetic acid
THF: tetrahydrofuran
TPP: tetraphenylporphyrin

1. Introduction and aims

In modern synthetic chemistry asymmetric synthesis bears of crucial importance. As enantiomers might exert different biological activity enantioselective synthesis is especially important in the field of pharmaceuticals but also concerning agricultural chemicals, flavors and fragrances. Several approaches are known to obtain enantiomerically pure compounds starting from achiral substances. One possibility is the application of chiral auxiliaries. The most serious drawback of chiral auxiliaries is that they need to be applied in stoichiometric amount and also they need to be removed which means an additional step in the synthesis. A more elegant method is the application of chiral catalysts which possesses none of the aforementioned disadvantages: they can be continually regenerated making their application more economic.¹ There is a consistently growing demand for new asymmetric synthesis methods and even more for the design of new, selective chiral catalysts.

Considering the choice of chiral catalyst in the industry, apart from its selectivity, the price is the most important factor. Chiral monoterpenes are widely used starting materials of stereoselective syntheses.^{2,3} They are produced by various plants in enantiomerically pure form in relatively great quantities and can be easily isolated therefore they are relatively inexpensive compared to other chiral synthons. Their double bonds, oxo- and hydroxyl groups make them well functionalizable while their already existing asymmetry center or centers might facilitate the stereoselective formation of new stereocenters via chiral induction.

In recent years it was found that chiral bi- and trifunctional compounds derived from monoterpenes *eg.* aminoalcohols and aminodiols may serve as excellent asymmetric catalysts.⁴ The constrained skeletons of bicyclic derivatives may contribute to the chirality transfer.

The present PhD work was focused on the synthesis of a chiral monoterpene-based compound library via stereoselective synthesis containing bi- and trifunctional compounds: aminoalcohols, aminodiols and diaminoalcohols starting from naturally occurring terpenes as chiral sources (Figure 1). We also intended to investigate the ring closure abilities of the prepared compounds to gain 1,3-heterocycles. Another goal was to apply the obtained compounds as chiral ligands in the reaction of benzaldehyde and diethylzinc and to gain information on the chiral induction of our potential catalysts.

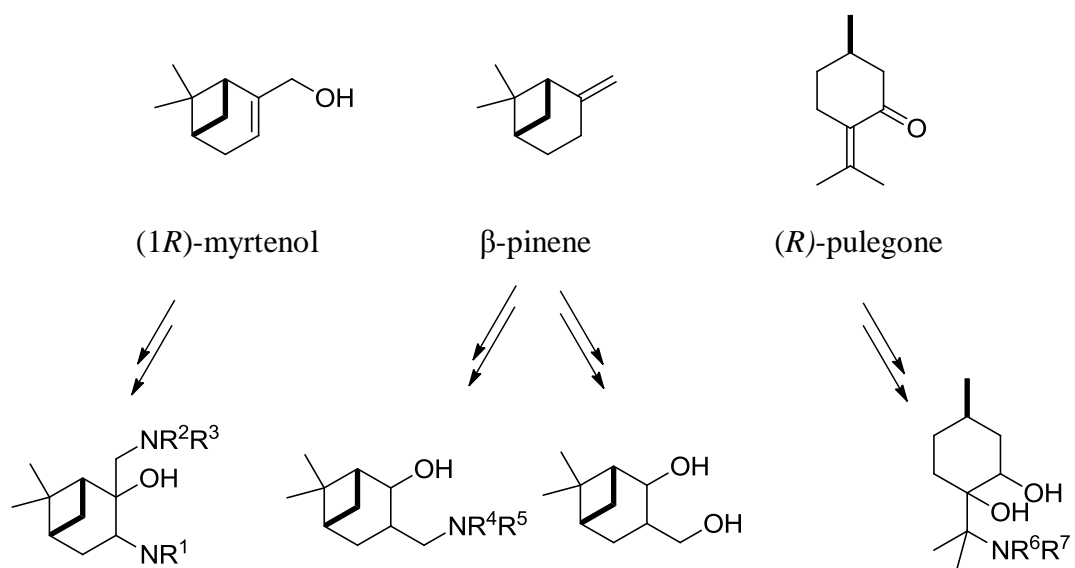


Figure 1.

2. Literature survey

Since the Institute of Pharmaceutical Chemistry has gained considerable experience in the synthetic elaboration of 1,3-aminoalcohols and a significant number of papers ⁵⁻¹⁰ have been published and also it has been intensively discussed in several dissertations (Szilvia Gyónfalvi, 2008; Árpád Balázs, 2010), the current literature survey is focused on the synthesis and application of chiral aminodiols and diaminoalcohols.

2.1 Synthesis and importance of chiral alicyclic 1,3-aminoalcohols

2.1.1 Synthetic strategies

Several strategies have been developed for the synthesis of alicyclic 1,3-aminoalcohols. For example one frequently applied method is the stereoselective Mannich-condensation and the subsequent diastereoselective reduction (**IV**, **V**).^{11, 12} Another synthetic possibility to obtain 1,3-aminoalcohols is aza-Michael-addition performed on α,β -unsaturated esters and the subsequent reduction of the resulting β -aminoesters (**II**).¹³⁻¹⁵

Reduction of chiral β -amino acids and esters prepared by classical or enzymatic resolution also results in the 1,3-aminoalcohol moiety (**II**).^{5, 6, 16-18} Hydrogenolysis and acid or base catalyzed ring opening of beta-lactams with the following reduction is also a popular method for the preparation of γ -aminoalcohols (**I**).^{5, 7, 19, 20} β -hydroxynitriles (**III**) and dihydrooxazines (**VI**) are also proved to be excellent starting materials.^{8, 10, 21-23}

Figure 2. presents the most applied synthetic strategies to obtain alicyclic 1,3-aminoalcohols.

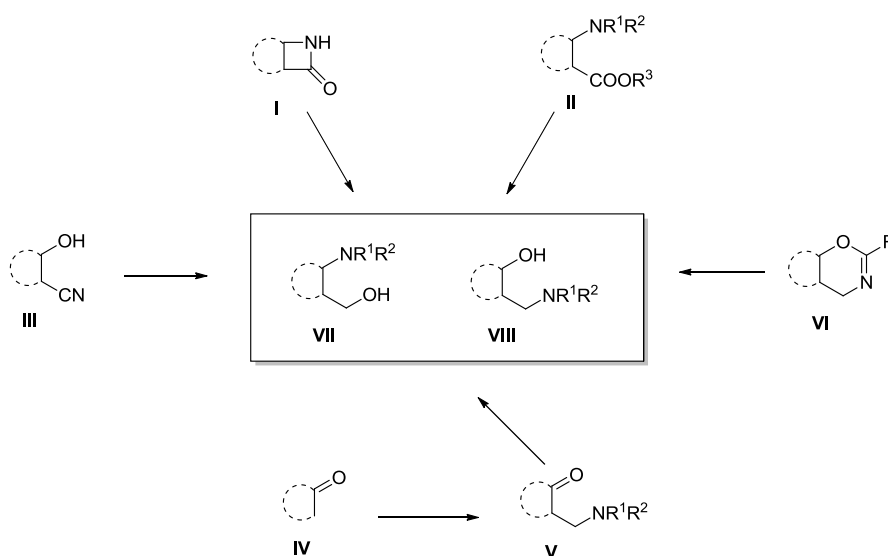


Figure 2.

2.1.2 Chemical importance – chiral auxiliaries and catalysts

The role of 1,3-aminoalcohols as chiral starting materials, auxiliaries and catalysts has been extensively investigated throughout the last decades.^{2,4}

In the recent years the synthesis of several γ -aminoalcohols has been reported starting from commercially available enantiopure monoterpenes: (+)-3-carene (**IX**), α -pinene (**X**), (+)-pulegone (**XI**), (+)-camphor (**XII**), (+)-fenchone (**XIII**). In 1987 Eliel et al. reported the three step synthesis of 8-aminomenthol (**XVI**, Eliel-aminoalcohol).²⁴ Since its report, the Eliel-aminoalcohol became exceptionally widely used in asymmetric synthesis as it can be easily converted into a variety of useful compounds (**XIX-XXII**) (Figure 3).^{4, 25-28}

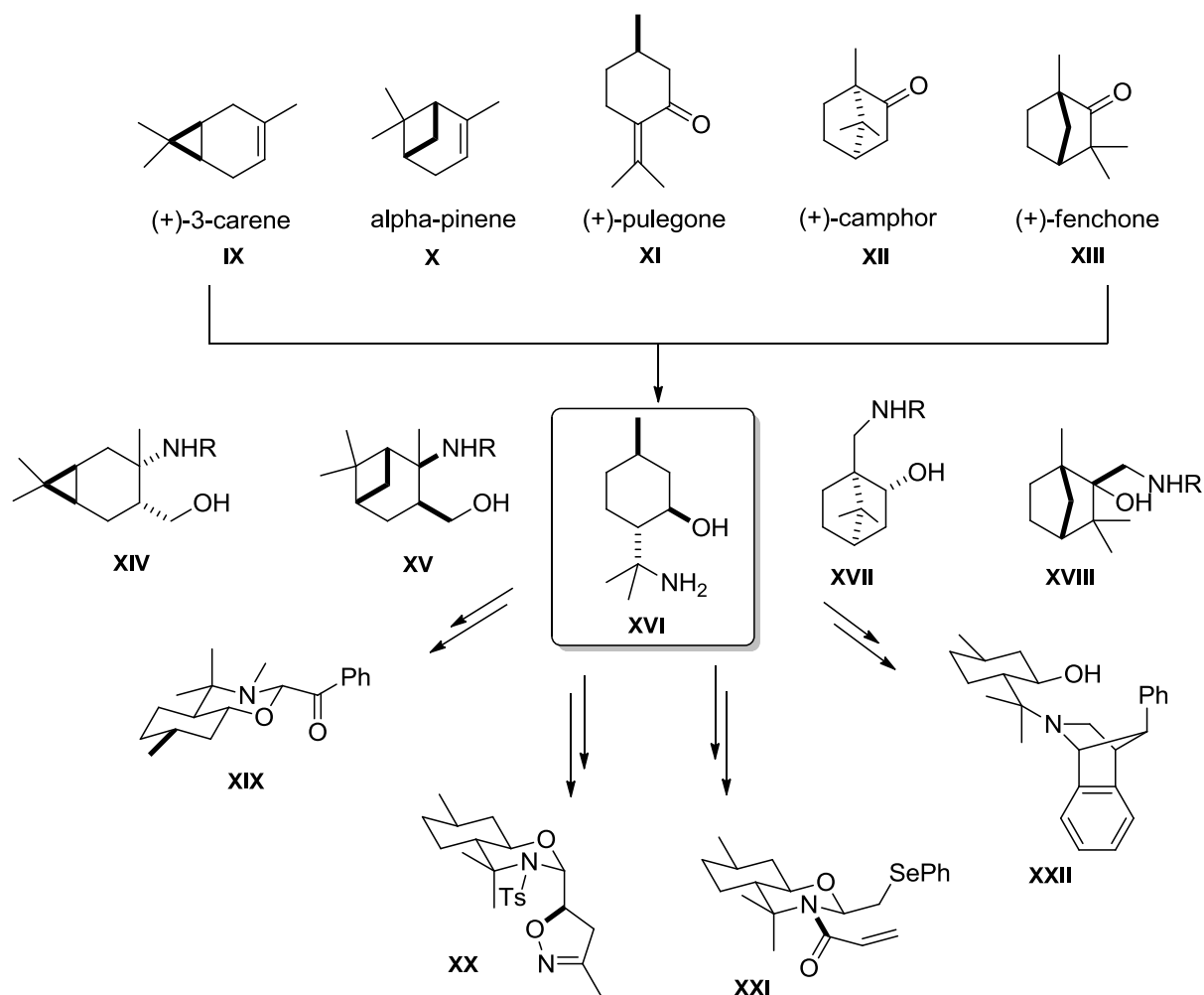


Figure 3.

Alicyclic 1,3-aminoalcohols play diverse role in asymmetric synthesis as chiral catalysts and auxiliaries.⁴ Their derivatives can be applied in enolate alkylation reactions^{29,30}, aldol

reactions³¹ but they also can be used as chiral phase transfer catalysts.³² Application of alicyclic 1,3-aminoalcohols in various pericyclic reactions has also been thoroughly investigated, their successful use in Diels-Alder reactions³³⁻³⁶, 1,3-dipolar cycloadditions^{28,37} and also in intramolecular Alder-Ene reactions have been reported.³⁸ They also proved to be useful in palladium catalysed allylic alkylations³⁹⁻⁴¹ and in Heck-reactions⁴² as catalysts and they also have a significant role in rhodium catalysed catalytic hydrogenation reactions.⁴³

The most investigated and frequent application of alicyclic 1,3-aminoalcohols is stereoselective nucleophilic addition of organozinc reagents to various aldehydes and ketones.⁴⁴⁻⁴⁷ Pedrosa et al. reported the synthesis of ferrocenyl derivatives prepared from 8-aminomenthol and their application in the addition of diethylzinc to various aldehydes and ketones with good enantioselectivity.⁴⁸ The addition of divinylzinc to aldehydes was investigated by Oppolzer and Radinov in the presence of a camphor-based aminoalcohol as chiral ligand.⁴⁹ The 1,3-aminoalcohol moiety can also aid the synthesis of chiral sulfoxides from the corresponding sulfides.⁵⁰ The application of enantiopure 1,3-aminoalcohols as substrates has also been reported for diastereoselective Ugi reactions.⁵¹

2.1.3 Pharmacological importance

The γ -aminoalcohol moiety can often be found in compounds showing pharmacological activity. Tramadol (**XXIII**), for example is an important opioid-type analgetic used in the treatment of severe pain.⁵² Vildagliptine (**XXIV**), also bearing the γ -aminoalcohol backbone is an oral DPP-4 inhibitor widely used in the antidiabetic therapy⁵³, while desvenlafaxine (**XXV**) exerts antidepressant activity.⁵⁴ Naturally occurring γ -aminoalcohol, sedamine (**XXVI**) – an alkaloid isolated from *Sedum acre* – also shows biological activity and is used in the treatment of cognitive disorders.^{55, 56}

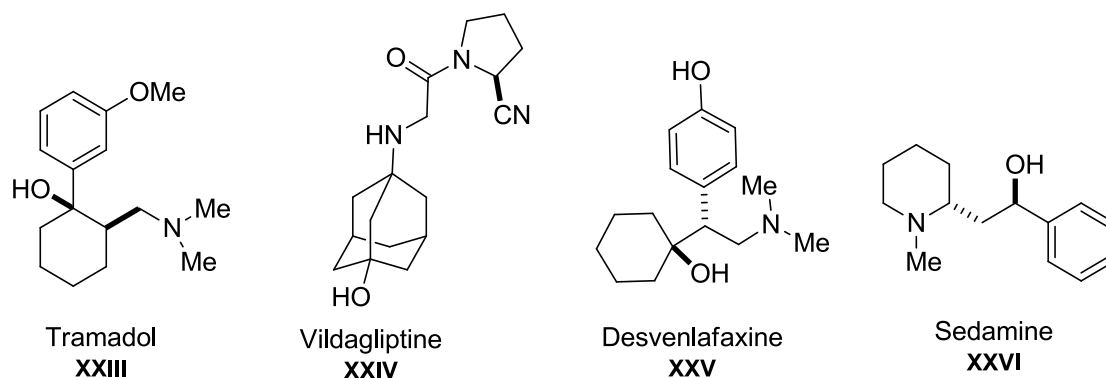


Figure 4.

2.2 Synthesis and importance of chiral 3-amino-1,2-diols

2.2.1 Synthetic strategies

As their chemical and pharmacological importance is indisputable, a number of strategies have been developed for the synthesis of chiral 3-amino-1,2-diols. The most frequent starting materials are allylic alcohols as they can easily be converted to allylic amines via Overman-rearrangement. Due to the nucleophilicity of the unsaturated C-C-bond of protected allylic amines they can readily be converted to epoxide, whose hydrolysis results in the aminodiol structure.⁵⁷ An alternative pathway is the *syn* or *anti* dihydroxylation of the allylic double bond.^{58, 59}

Sharpless epoxidation of allylic alcohols and the subsequent regioselective azido- or aminolysis also might result in the 3-amino-1,2-diol structure.⁶⁰⁻⁶² An alternative strategy – also starting from allylic alcohols – is the activation of the hydroxyl group by mesylation or tosylation followed by dihydroxylation and Mitsunobu-reaction: the resulting azido functional group can easily be converted to obtain the 3-amino-1,2-diol moiety.⁶³

2.2.1.1 Aminolysis of 2,3-epoxyalcohols

The most general process for the stereoselective synthesis of 3-amino-1,2-diols is the regioselective aminolysis of 2,3-epoxyalcohols.

In 1985 Caron and Sharpless reported titanium(IV) isopropoxide mediated regioselective nucleophilic opening of 2,3-epoxyalcohols.⁶⁴ It was found that coordination of the metal alkoxide to the oxygen in epoxyalcohols facilitates the ring opening reaction as well as contributes to the regioselectivity of the reaction: a strong preference is observed for C3 as the site of nucleophilic attack. A wide range of nucleophiles have been tested, however, aminolysis performed with primer amine *n*-butylamine resulted in no observable product. In 1991 Canas and co-workers reported successful titanium(IV) mediated regioselective ring-opening of chiral 2-3-epoxyalcohols with primary amines resulting in the 3-amino-1,2-diol moiety.⁶¹

Wang et al. reported the enantioselective synthesis of 3-amino-1,2-diols (**XXIX**) starting from racemic epoxyalcohols applying a tungsten/*bis*(hydroxamic acid) catalytic system. The reactions performed with aromatic and aliphatic amines proceeded with high enantioselectivity (up to 95 % *ee*) and excellent regioselectivity (Figure 5).⁶⁰

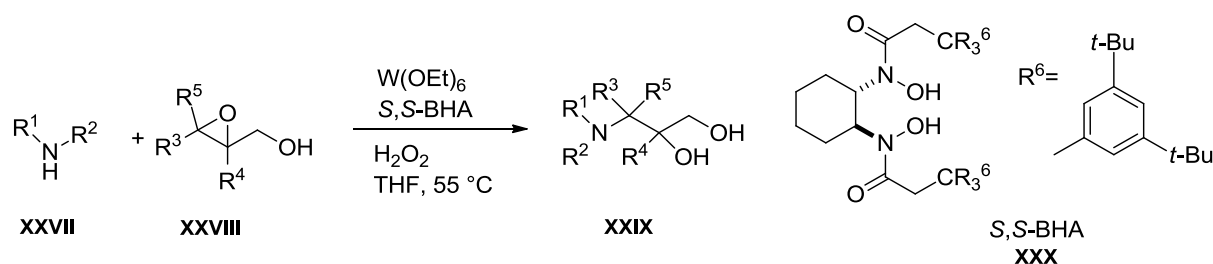


Figure 5.

A library of carane- and pinane-based 3-amino-1,2-diols was synthesised starting from commercially available (+)-3-carene (**IX**) and α -pinene (**X**). First, monoterpene-based allylalcohols (**XXXII**) were prepared according to literature method. Epoxidation of the allylalcohols proceeded stereoselectively in both cases, resulting in key intermediate epoxyalcohols (**XXXIII**). Regioselective aminolysis of the oxirane ring in the presence of LiClO₄ with primary and secondary amines resulted in monoterpene-based aminodiols libraries (**XXXIV**). The regioselectivity of ring closure reactions was also investigated. In the case of carane-based aminodiols the formation of the oxazine ring was exclusive (**XXXV**), whereas in the case of pinane-based aminodiols the selective formation of the oxazolidine ring was observed (**XXXVI**) (Figure 6).^{62,65,66}

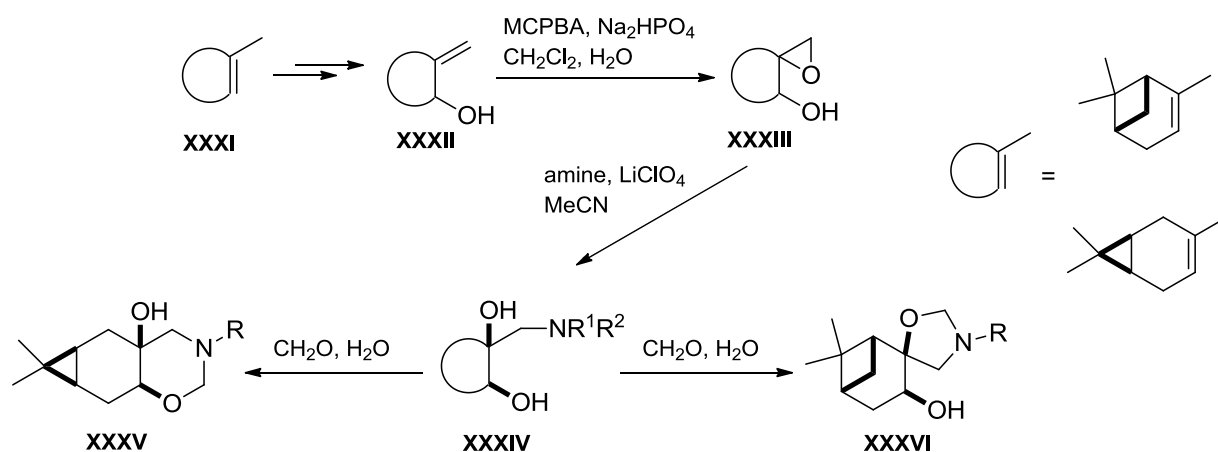


Figure 6.

Anticonvulsant drug – Vigabatrin (**XLI**) is marketed in racemic form although the *S* enantiomer functions as the eutomer. Alcón et al. reported the stereoselective synthesis of protected (*S*)-Vigabatrin starting from enantiomerically enriched epoxyalcohol (**XXXVII**) applying regioselective aminolysis as synthetic strategy to form key intermediate 3-amino-1,2-diol (**XXXVIII**).⁶⁷ Hydrogenolysis of the benzyl group and subsequent Boc protection led to

aminodiol intermediate. After the protection of the hydroxyl groups oxidation was performed in the presence of RuCl_3 with NaIO_4 and the corresponding acid was transformed into its methyl ester (**XXXIX**). Deprotection and Corey-Hopkins deoxygenation resulted in target *N*-Boc Vigabatrin methyl ester (**XL**) (Figure 7).

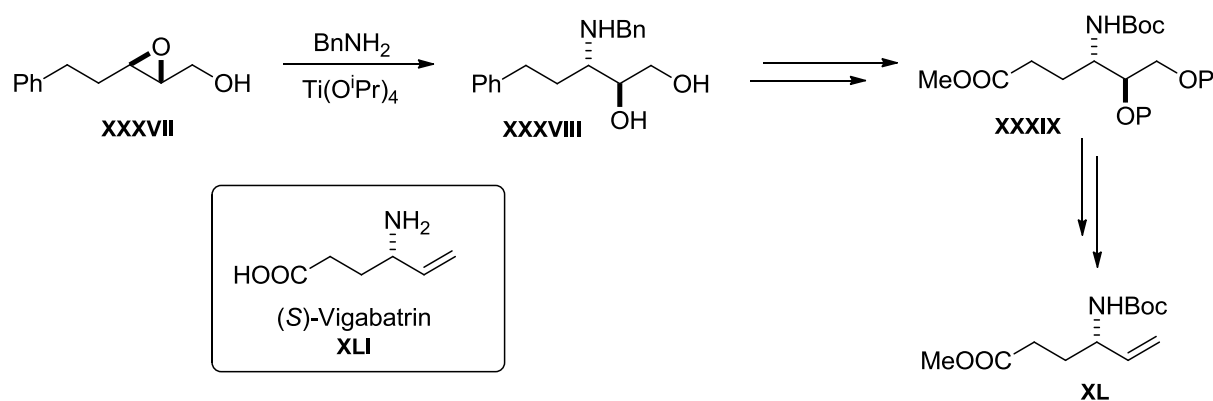


Figure 7.

2.2.1.2 Stereoselective dihydroxylation of allylic amines

Stereoselective dihydroxylation by OsO_4 is a typical synthesis method for 3-amino-1,2-diols starting from *N*-protected allylic amines. A carane-based compound library has been synthesized starting from bicyclic aldehyde **XLII** obtained from natural *S*-(-)-perillaldehyde. Reductive amination of **XLII** yielded key intermediates allylamine **XLIII**, **XLIV**. In order to investigate the effect of the protecting group on the stereoselectivity of the dihydroxylation reaction the amino function was protected by Cbz as well as Boc. The dihydroxylation was performed with catalytic amount of OsO_4 in the presence of stoichiometric amount of NMO. In both cases the reaction proceeded with excellent stereoselectivity and yield (Figure 8).⁵⁸

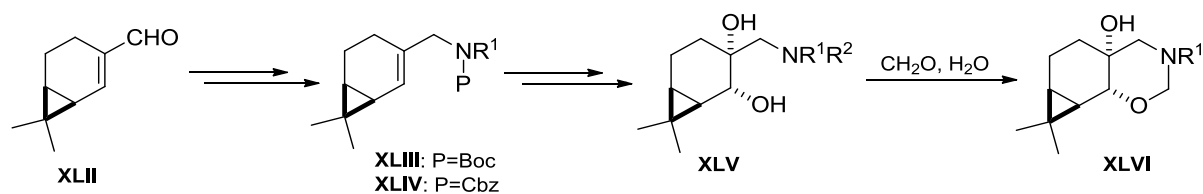


Figure 8.

In those cases when the starting material contains no chiral center or the existing asymmetry shows no chiral induction in the dihydroxylation stereoselectivity can be enhanced by applying chiral additives. AD mix α and β are commercially available reagent mixtures applied in

dihydroxylation reactions as chiral catalysts.⁶⁸ In 2007 Narina et al. reported the stereoselective synthesis of (*S*)-timolol (**XLIX**). The aminodiols subunit (**XLVIII**) of the target compound was formed by AD mix α (*ee* = 56 %, Figure 9).⁶⁹

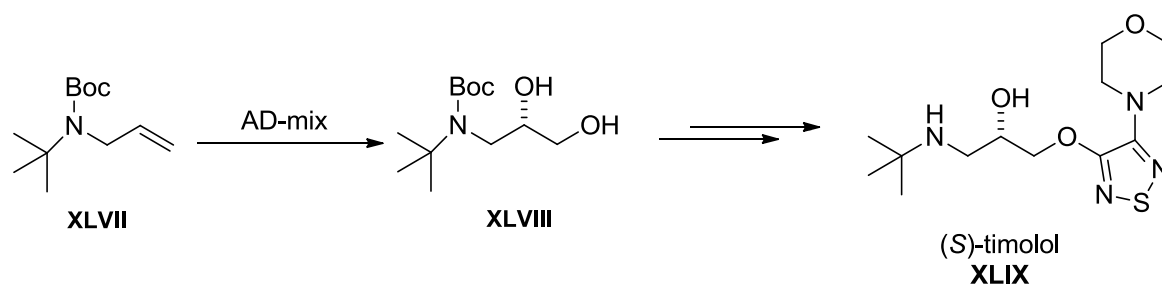


Figure 9.

Miao and co-workers examined the chiral catalytic behaviour of OsO₄-wool complex in the dihydroxylation of olefins and allylamines. They prepared a stable, reusable OsO₄-wool complex and applied it as chiral catalyst with good selectivity (up to *ee* = 84 %).⁷⁰

2.2.1.3 Other methods

Rigoli et al. developed a highly diastereoselective Ru-catalysed synthesis method for the 3-amino-1,2-diol moiety starting from variously substituted homoallenic carbamates (**L**). The relative anti-stereochemistry between the amino group and the vicinal diol function proposed to be the result of 1,3-bischelation of the metal in the transition state (Figure 10).⁷¹

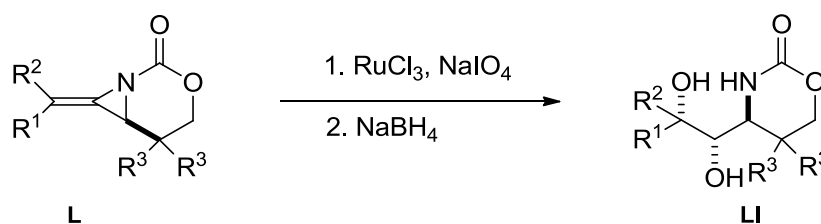


Figure 10.

In 2010 a german research group reported the synthesis of a pinane-based 3-amino-1,2-diol (**LIII**) via a photoinduced azidohydroperoxidation reaction starting from β -pinene (**LII**). Applying the same strategy they also prepared regioisomeric aminodiol (**LIV**) derived from α -pinene (**X**) (Figure 11).⁷²

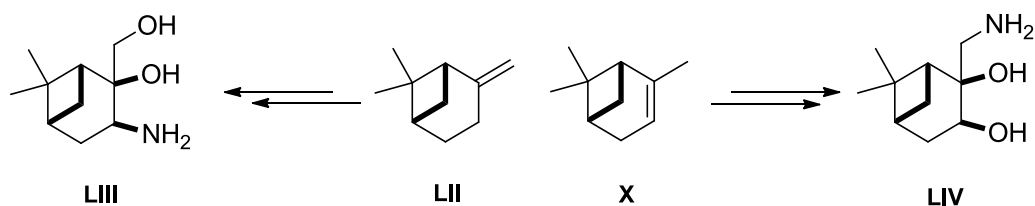


Figure 11.

Another synthetic strategy incorporates the stereocontrolled addition of organometallic compounds to imines derived from chiral α -aryloxyaldehydes. Polt et al. utilised Schiff-base of L-alanine methylester (**LV**). Grignard-type alkylation of the Schiff base resulted in an easily separable diastereomer mixture (**LVI**, **LVII**). *O*-protection as pivalate and the subsequent dihydroxylation furnished protected triol **LIX**. The primary alcohol function was oxidized using NaOCl and TEMPO as catalyst. Reductive intramolecular alkylation of the resulting crude aldehyde afforded the pyrrolidine derivative **LX** (Figure 12).⁷³

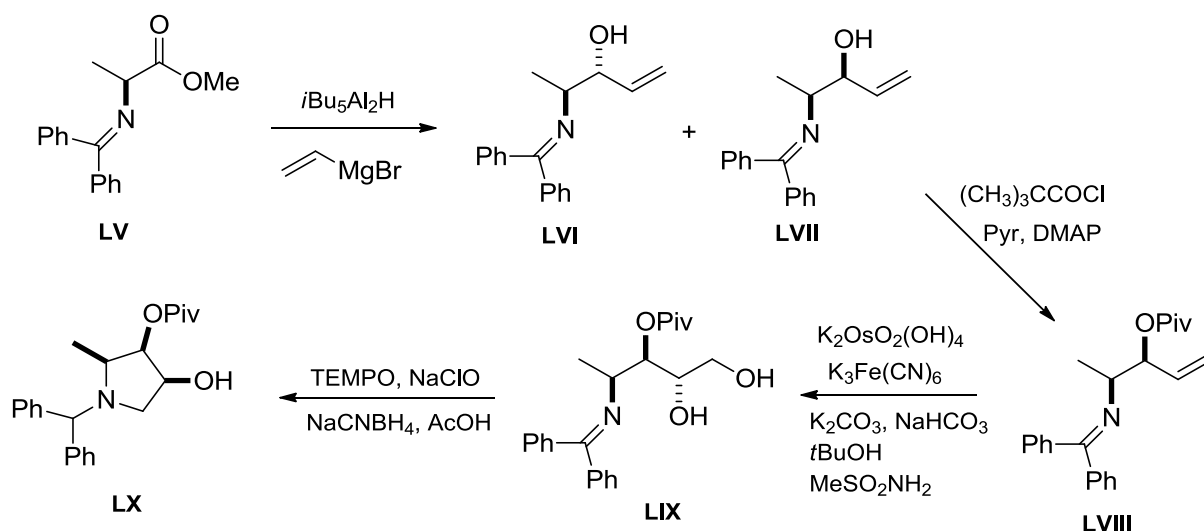


Figure 12.

2.2.2 Application of chiral 3-amino-1,2-diols

2.2.2.1 Chiral 3-amino-1,2-diols as asymmetric catalysts

Asymmetric tridentate ligands, such as aminodiols may serve as excellent chiral catalysts in the most diverse asymmetric reactions. Their enantioselective catalysis is reported in the literature in allylic alkylations (method C), in the transfer hydrogenation of ketones (method A). 3-Amino-1,2-diols are also applied as chiral modifiers in the reduction of ketones with LiAlH_4 . However, the main application area is the enantioselective addition of organozinc reagents to aldehydes and imines (method B) (Figure 13).

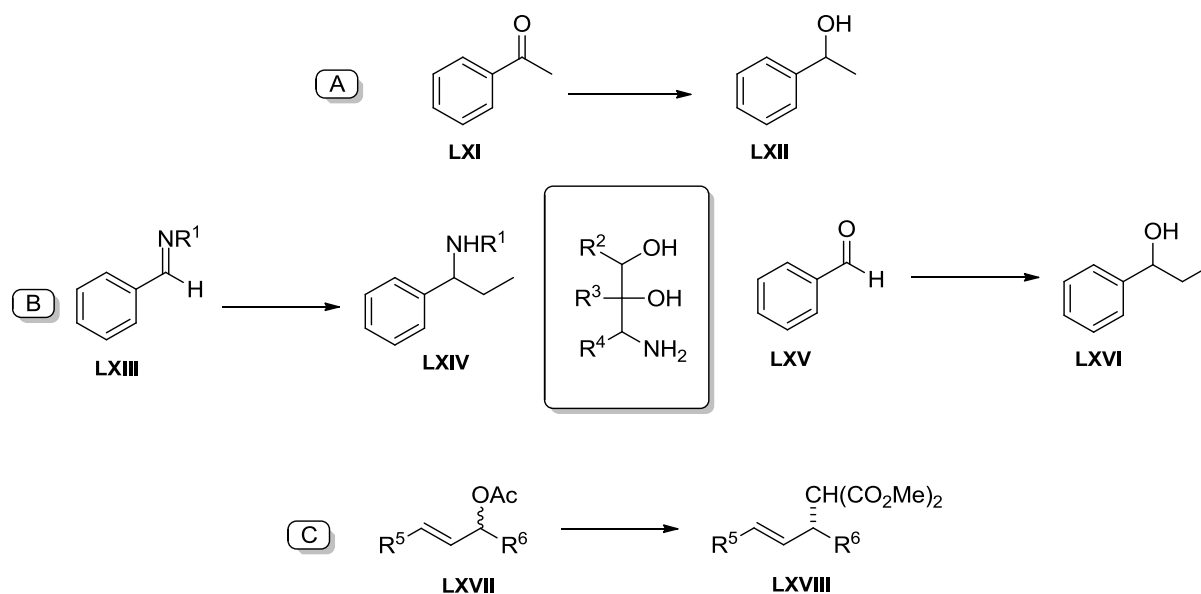


Figure 13.

In 2007 Pericàs et al. reported the synthesis of phosphinooxazolines derived from 3-amino-1,2-diols and their palladium complexes have been applied as chiral mediators in asymmetric allylic alkylation reactions. The synthesis started from Sharpless epoxyethers (**LXIX**) and 3-amino-1,2-diols (**LXX**) were obtained via aminolysis. Then the phosphinooxazoline structure was formed in several steps followed by the Pd-complexation. After optimization the chosen mediator was used in asymmetric allylic alkylations on a wide range of substrates with excellent results (up to $ee = 98\%$, Figure 14).⁷⁴

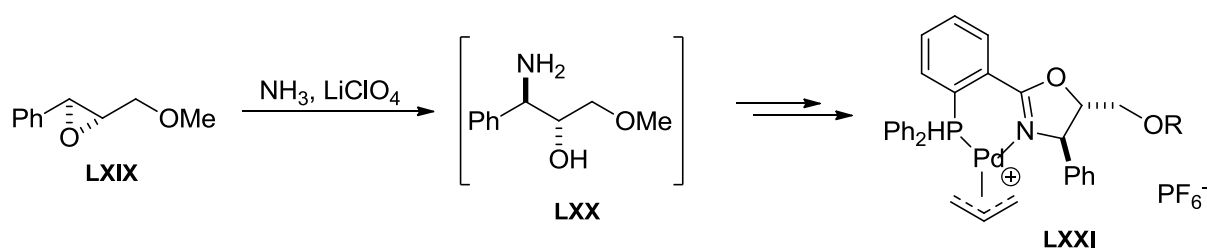


Figure 14.

As enantiomerically pure secondary alcohols are valuable starting materials of chiral syntheses, their production from prochiral ketones is a field of intensive research. Pericàs also applied similarly prepared variously substituted simple 3-amino-1,2-diols (**LXXII**) in catalytic transfer hydrogenation reactions of prochiral ketones in the presence of Ru-containing catalyst. Good enantioselectivity was achieved (up to $ee = 72\%$) (Figure 15).⁷⁵

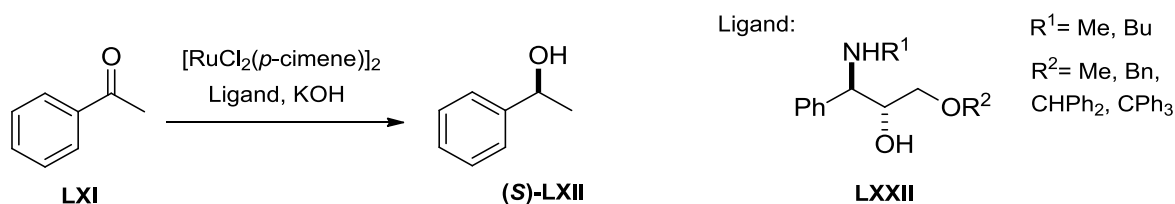


Figure 15.

Lu et al. prepared chiral, pinane-based 3-amino-1,2-diols derived from (1*R*)-(-)-myrtenol. The obtained aminodiols (**LXXV**, **LXXVI**) were applied as chiral modifiers for asymmetric reduction of a wide range of aryl and alkenyl-methyl ketones. Moderate to good enantioselectivities (up to *ee* = 91%) exclusively with *R* selectivity were measured with good yield (Figure 16).^{76,77}

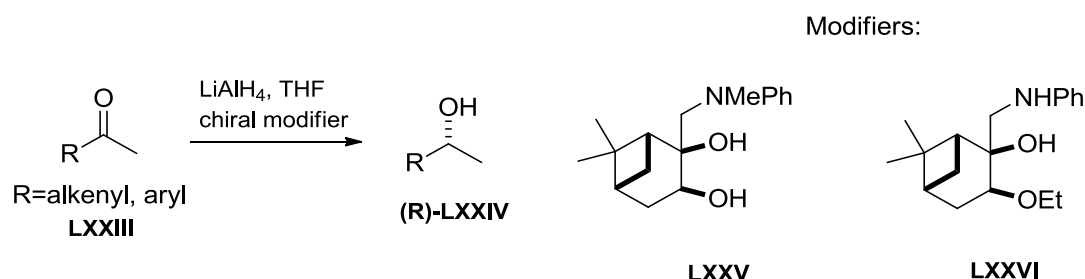


Figure 16.

The most studied reaction regarding 3-amino-1,2-diols as chiral catalysts is the enantioselective addition of organozinc reagents to prochiral aldehydes, more precisely the nucleophilic reaction of diethylzinc and benzaldehyde as model reaction.

Riera et al. in 1997 reported the synthesis of an enantiomerically pure aminodiol library starting from cinnamylalcohol. A total of 19 derivatives were prepared and applied in the model reaction. They found that the bulkyness of the alkoxy-group and the *N* incorporated in a six membered ring are the key parameters of high catalytic activity (Figure 17).⁷⁸

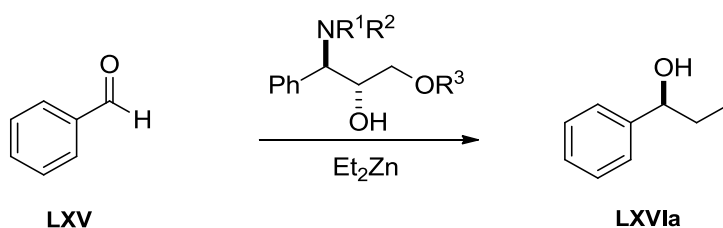


Figure 17.

Lu et al. synthesized pinane-based tridentate ligands (**LXXVIII**) derived from (1*R*)-(-)-myrtenol (**LXXVII**). Their application in the addition of diethylzinc to benzaldehyde proceeded with moderate to good enantioselectivity (up to *ee* = 88%, Figure 18).⁷⁹

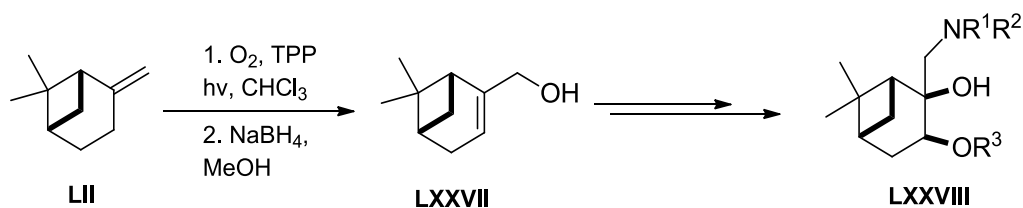


Figure 18.

A bulgarian research group reported the synthesis of 3-amino-1,2-diols with camphane skeleton (**LXXXII**). Starting from commercially available 10-camphorsulfonyl chloride (**LXXIX**) diastereomeric mixture of epoxides was prepared and after successful separation their configuration has been determined. (**LXXX**). In both cases the aminolysis proceeded regioselectively resulting in compounds **LXXXI**. Subsequent reduction of the carbonyl function with LiAlH_4 proceeded without stereoselectivity resulting in compounds **LXXXII**. The obtained potential catalysts were tested showing moderate stereoselectivity in the model reaction (Figure 19).⁸⁰

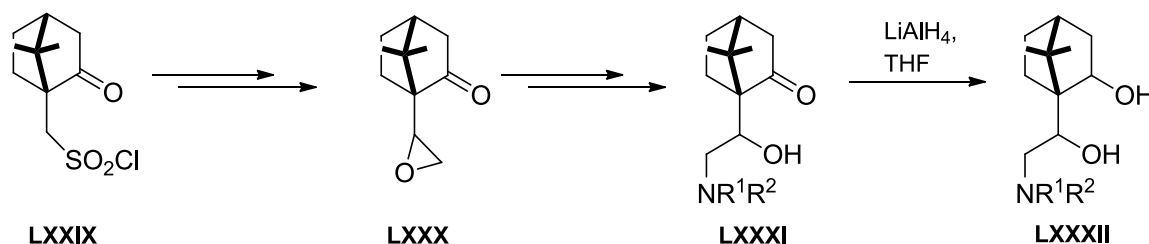


Figure 19.

Many excellent chiral catalysts have been developed for the model reaction of aromatic aldehydes and diethylzinc, however the analogous addition of organozinc reagents to imines remained neglected. Riera et al. applied 3-amino-1,2-diols (**LXXXIV**) as chiral catalysts and silylating agents as Lewis acid additives in the addition of diethylzinc to aryl diphenylphosphinoyl imine (**LXXXIII**) achieving good enantioselectivity (Figure 20).⁸¹

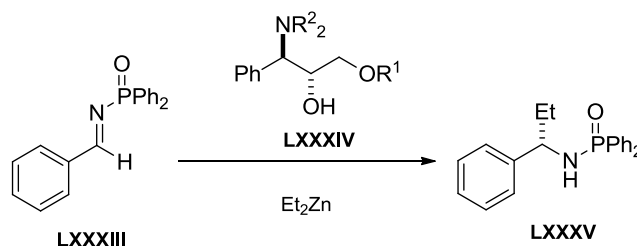


Figure 20.

2.2.2.2 Chiral 3-amino-1,2-diols as building blocks

Nucleosides are crucial building blocks in all living systems while their analogues might exert antitumor or antiviral activity. Substitution of the furanose ring by a hydrocarbon ring results in resistance against enzymatic degradation.⁸² Chiral 3-amino-1,2-diols might also serve as building blocks in the synthesis of carbocyclic nucleoside analogues bearing with anticancer or antiviral activity.^{83,84}

In 2010 Szakonyi and Fülöp et al. reported the synthesis of a chiral pinane-based sterically constrained nucleoside library (**LXXXVIII-XC**, Figure 21).^{65,85}

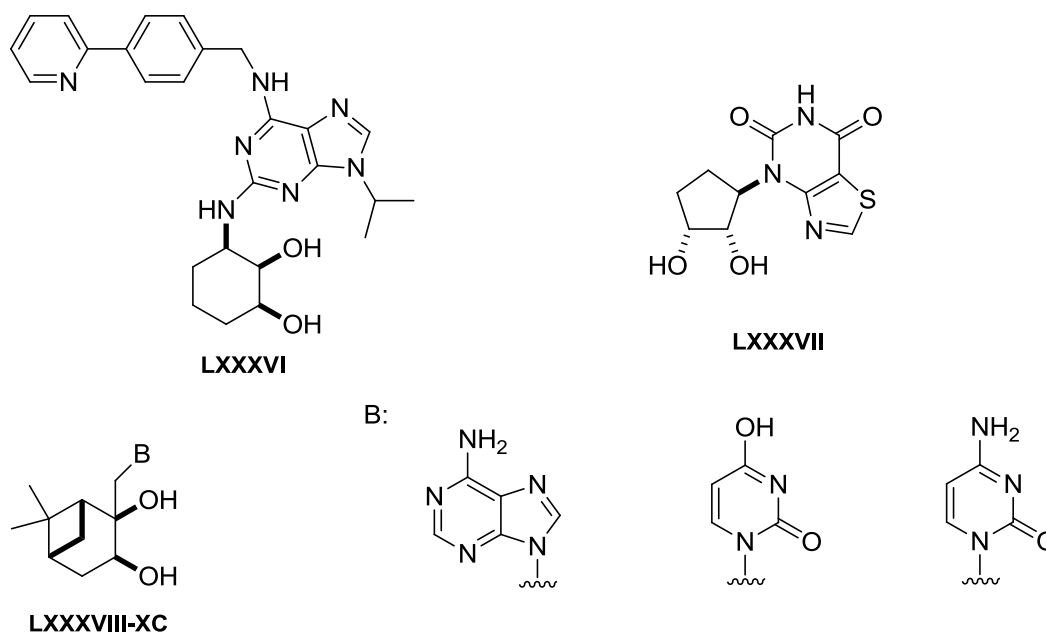


Figure 21.

2.2.3 Pharmacological importance of chiral 3-amino-1,2-diols

The pharmacological importance of 3-amino-1,2-diols and their derivatives is remarkable as they exert cardiovascular, cytostatic and antiviral effect.

The Abbott-aminodiol (**XCI**) can be found as part of many β -receptor antagonists, this moiety is believed to mimic the transition state for the renin-catalysed hydrolysis of angiotensinogen, therefore several derivatives were synthesized and tested for antihypertensive activity.⁸⁶ Zankiren® (**XCII**) and Enalkiren® are potent renin inhibitors.⁸⁷

β -Blockers, which can be regarded as aminodiol derivatives, such as propranolol (**XCIV**) and metoprolol (**XCVI**) are extensively used for the treatment of hypertension.⁸⁸

Apart from their cardiovascular application, aminodiols can also exert antidepressive activity: (*S,S*)-Reboxetine (**XCIII**) – a selective norepinephrine reuptake inhibitor – is approved in many countries for the treatment of unipolar depression.⁸⁸

The biological effect of some 3-amino-1,2-diols is still investigated, compound **XCIV** acts as a selective antagonist on receptor P2X₁⁸⁹, which is expressed in smooth muscle and platelets presumably contributing to sympathetic vasoconstriction in small arteries.⁹⁰

Cytosaxone (**XCVII**) is a naturally occurring heterocyclic aminodiol derivative isolated from *Streptomyces* species.⁹¹⁻⁹³ Cytosaxone expresses cytokine modulator activity by inhibiting the signaling pathway of Th2 cells hence it could be a valuable compound in the field of immunotherapy.^{94,95}

Aristeromycin (**XCVIII**), a naturally occurring carbocyclic nucleoside analogue exerts antibiotic, antiviral and antitumor activity.^{96,97}

Figure 22 represents the most important, pharmacologically active 3-amino-1,2-diol derivatives.

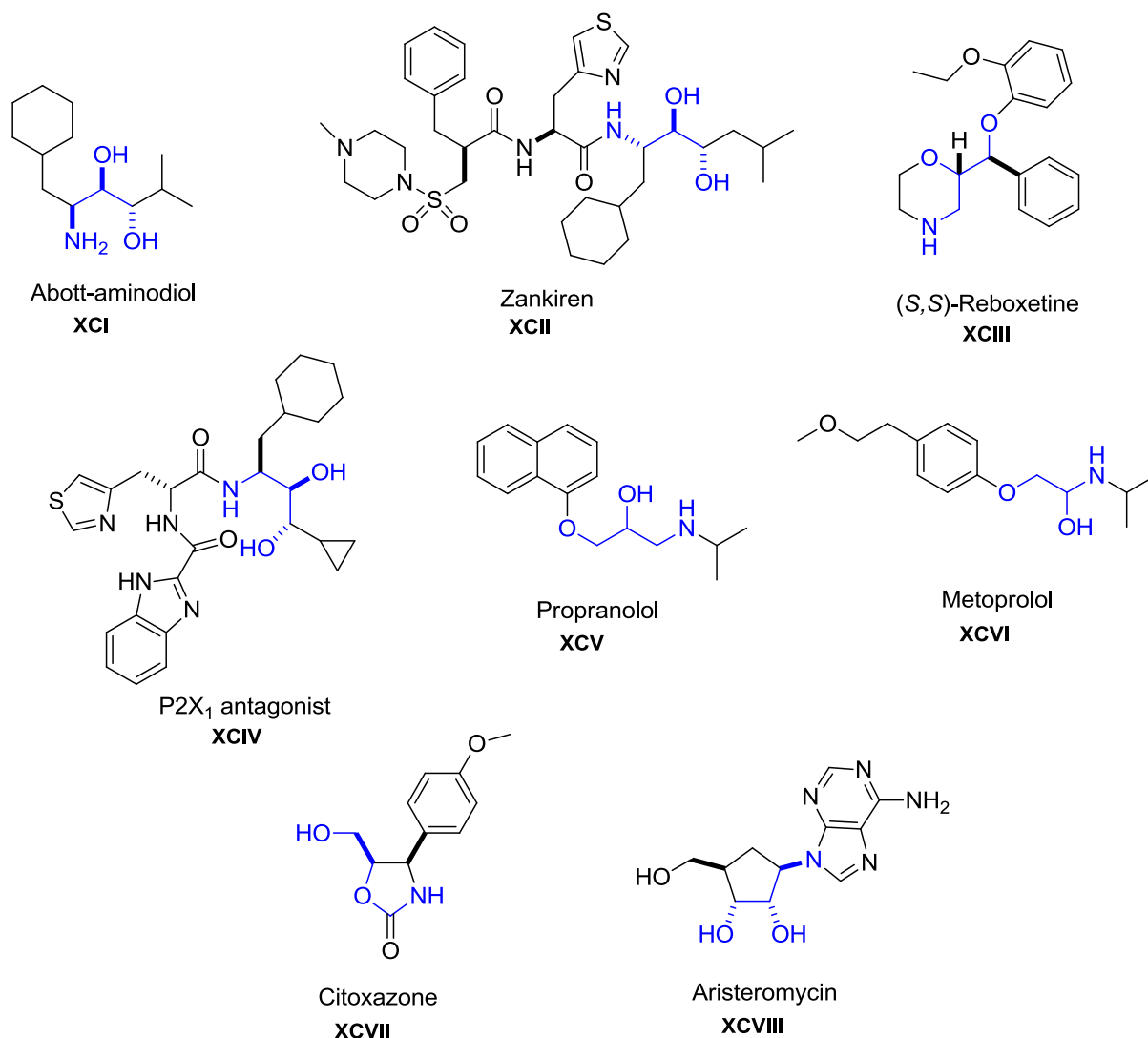


Figure 22.

Apart from their direct pharmacological application, 3-amino-1,2-diols can also serve as building blocks of biologically active compounds. Pastó et al. published the enantioselective synthesis of Boc-protected α -hydroxy- β -amino acid derivatives starting from *N*-Boc-protected 3-amino-1,2-diols. The prepared synthons can be used in the stereoselective synthesis of docetaxel (Taxotere®) (**CIV**), a widely used chemotherapeutic drug (Figure 23).^{98,99}

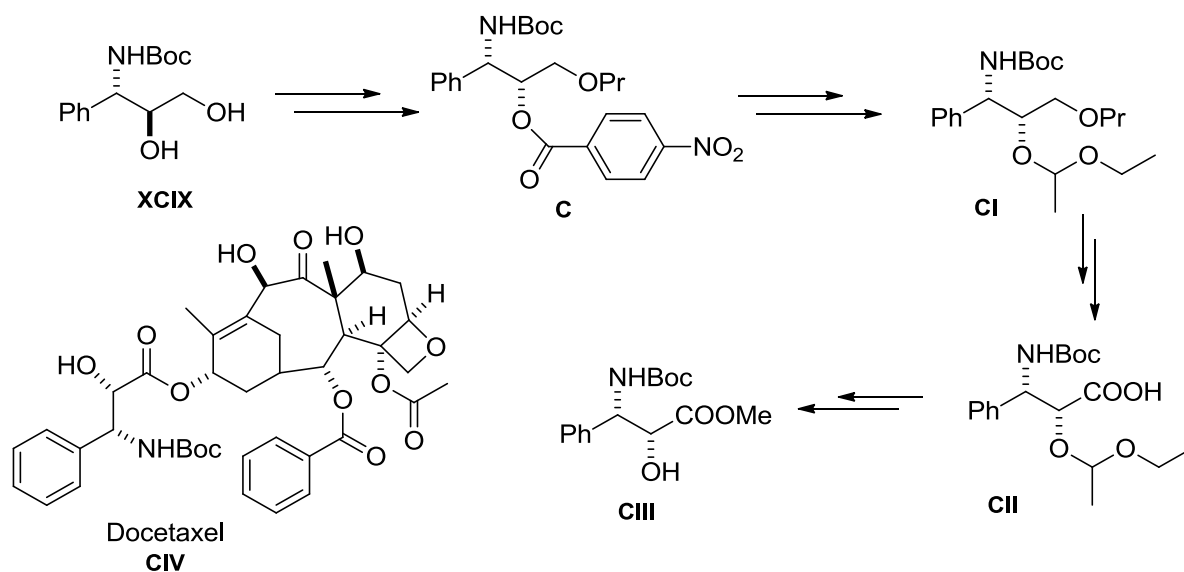


Figure 23.

2.3 Synthesis and pharmacological importance of chiral diaminoalcohols

2.3.1 Synthetic strategies

Numerous synthetic strategies are known for the development of the diaminoalcohol moiety. The most widespread method is aminolysis¹⁰⁰ or azidolysis^{101,102} (and subsequent reduction of the azido function) of *N*-protected amino epoxides. Another possibility is the opening of amino epoxides with nitriles via Ritter reaction and reduction of the obtained amides.^{103,104} Stereoselective reduction of enaminones also results in various diaminoalcohols.^{105,106}

α -Amino acids serve as excellent starting materials in the synthesis of diaminoalcohols: Bernadetti et al. reported the stereoselective synthesis of the diaminoalcohol core (CXI) of ritonavir (CXII) based on epoxyalcohol intermediates starting from α -amino acid methylester (CV). First *trans* enone (CVI) was synthesised via Horner-Emmons olefination, subsequent stereoselective reduction and *syn* epoxidation resulted in CVII. Regioselective reductive cleavage of the oxirane moiety afforded 1,3-*syn* diol CVIII. The key step of the synthesis of the diaminoalcohol moiety is the conversion of the hydroxyl group into azide (CIX). Finally catalytic hydrogenation of the azido function resulted in hydroxyethylene isostere CXI (Figure 24).¹⁰⁷

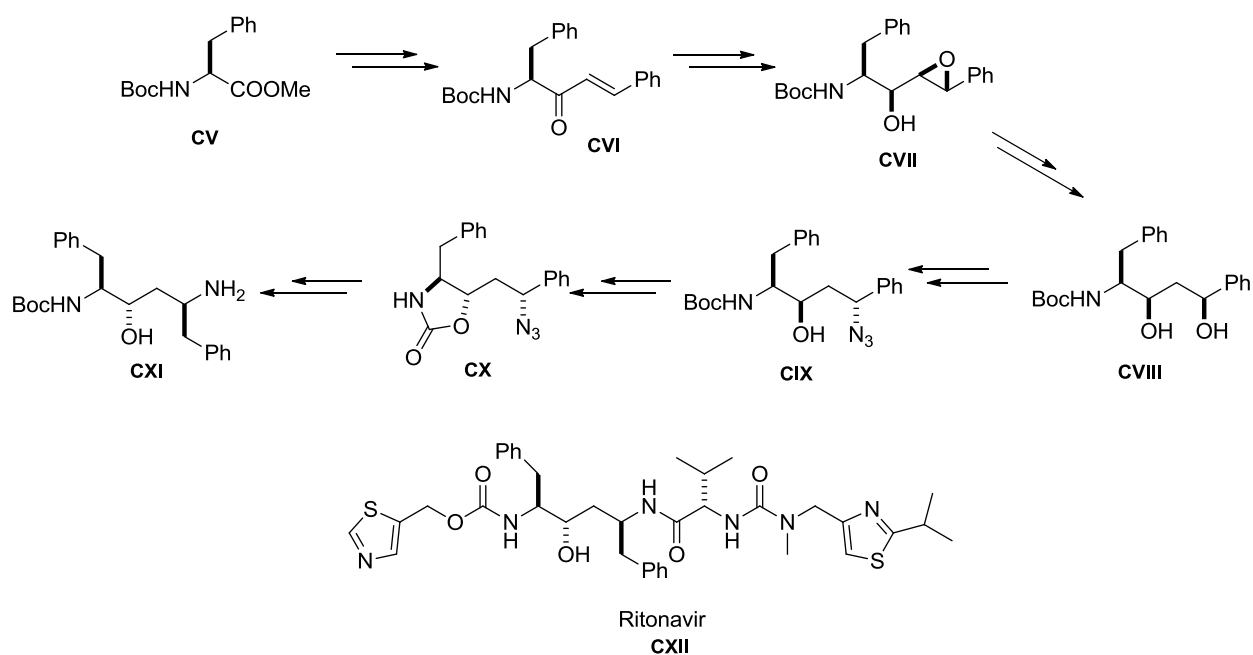


Figure 24.

Weyker et al. developed a synthesis method – applying L-phenylalanine (**CXIII**) as starting material – for the production of a urea derivative of diaminoalcohol **CXVI** used for the preparation of HIV protease inhibitors. The key protected epoxide (**CXV**) was prepared in several steps, subsequent aminolysis in isopropanol resulted in **CXVI** (Figure 25).¹⁰⁸

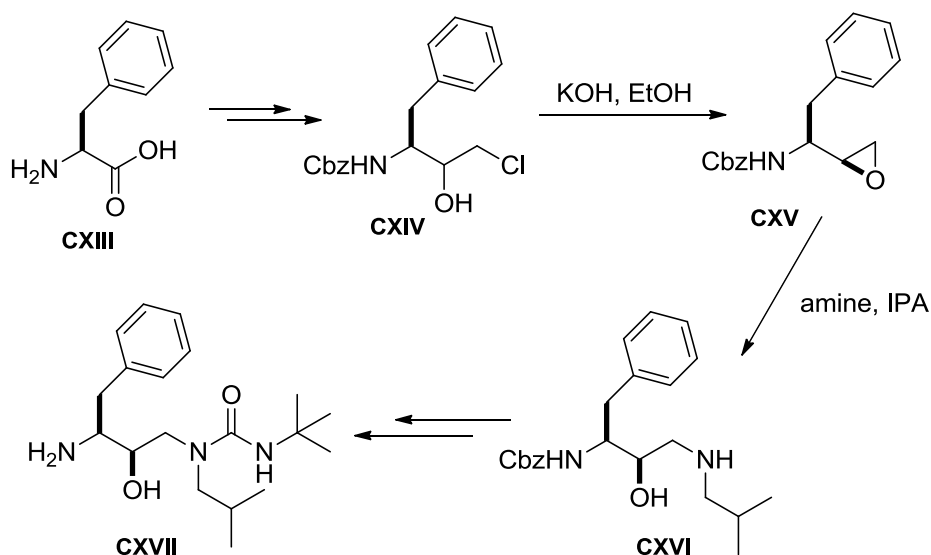


Figure 25.

Fu and Chen reported the synthesis of diaminoalcohols via stereoselective Ugi-reaction starting from α,α' -iminodiacetic acid analogues.¹⁰⁹ Reaction of nitroalkanes with α,β -unsaturated

aldehydes and subsequent catalytic hydrogenation can also lead to the aforementioned moiety.¹¹⁰

Rondot et al. reported the efficient regio- and stereoselective synthesis of diaminoalcohol derived dihydrooxazines (**CXIX**) from readily accessible aminodiol **CXVIII** via trichloroacetimidate intermediates. They also prepared protected forms of the diaminoalcohol moiety (Figure 26).¹¹¹

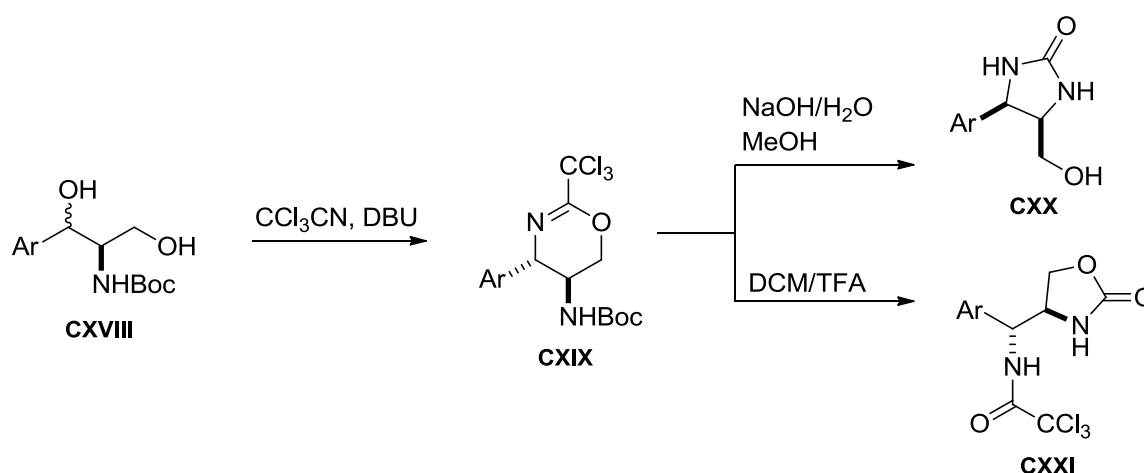


Figure 26.

Another synthetic strategy applies chiral sulfoxide chemistry. Zanda et al. reported the enantioselective synthesis of hydroxyethylamine isosteres. The reaction of lithiated β -sulfinylethylamines (**CXXIII**) and α -amino-sulfones (**CXXII**) afforded 2-sulfinyl-1,3-diamines (**CXXIV**). The target compounds were achieved by nonoxidative Pummerer-reaction of **CXXIV** with inversion of configuration (Figure 27).¹¹²

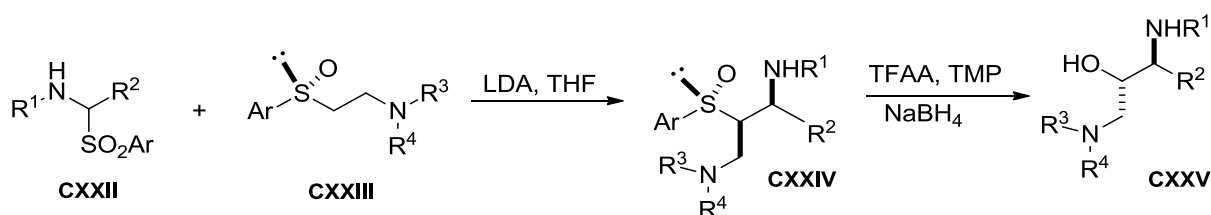


Figure 27.

2.3.2 Pharmacological importance

In the last decade numerous compounds bearing the diaminoalcohol moiety have been developed and found to exert pharmacological activity. Carter et al. lately discovered an orally bioavailable CC Chemokine Receptor 2 antagonist with an acyclic diaminoalcohol backbone (**CXXVI**).¹¹³ HIV-pretease inhibitor saquinavir (**CXXVII**) is an FDA approved oral drug used

in the treatment of HIV/AIDS in combination with other antiretroviral compounds.¹¹⁴ Diaminoalcohols also proved to be efficient in the treatment of Alzheimer's disease as exerting human β -secretase inhibitor activity (**CXXIX**).^{115,116}

Naturally occurring diaminoalcohols also have pharmacological activity: (-)-Balanol (**CXXVIII**), a metabolite produced by the fungus *Verticillium balanoides* proved to be effective inhibitor of Protein Kinase C (Figure 28).¹¹⁷

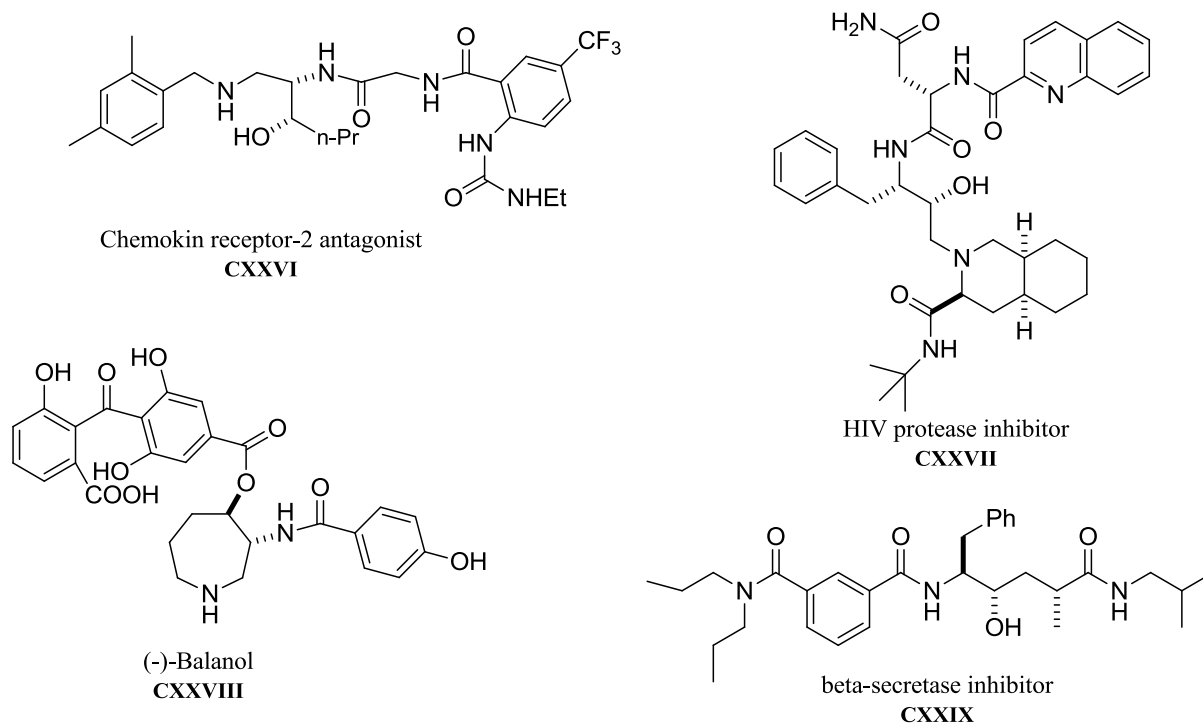


Figure 28.

2.3.3 Application of diaminoalcohols

Although the field of 1,2- and 1,3-aminoalcohols and aminodiols have lately been thoroughly investigated and exploited, the research area of diaminoalcohols remained nearly intact: very few chemical applications are mentioned in the literature.^{118,119}

A Japanese research group in 1974 reported the synthesis and characterization of binuclear and trinuclear copper(II) complexes starting from diaminoalcohols.¹²⁰

3. Results and discussion

3.1 Synthesis of pinane-based 1,3-aminoalcohols and diols

3.1.1 Synthesis of 1,3-aminoalcohols derived from (-)- β -pinene

Nopinone (**1**) was synthesized from commercially available (-)- β -pinene (**LII**) by modification of literature method: changing CCl_4 and MeCN mixture to EtOAc is a greener method and also afforded better yield.^{121,122} Nopinone was converted to Mannich-bases (**2-4**) in the presence of paraformaldehyde and amine hydrochlorides. When Mannich reaction was performed with dimethylamine hydrochloride moderate stereoselectivity was observed (according to NMR measurements $de = 70\%$) and the diastereomeric mixture proved to be inseparable (**2**).¹²³ In case of (*R*)-*N*-benzyl- α -methylbenzylamine hydrochloride the reaction proceeded stereoselectively but unfortunately with low yield (**4**). Applying dibenzylamine hydrochloride afforded the corresponding base in a highly stereoselective reaction with acceptable yield resulting in **3a** exclusively (Figure 29, Table 1).

Reduction of **3a** with LiAlH_4 also proceeded stereoselectively, resulting in the first 1,3-aminoalcohol analogue. The relative configuration of **5** was confirmed by 2D NMR measurements.

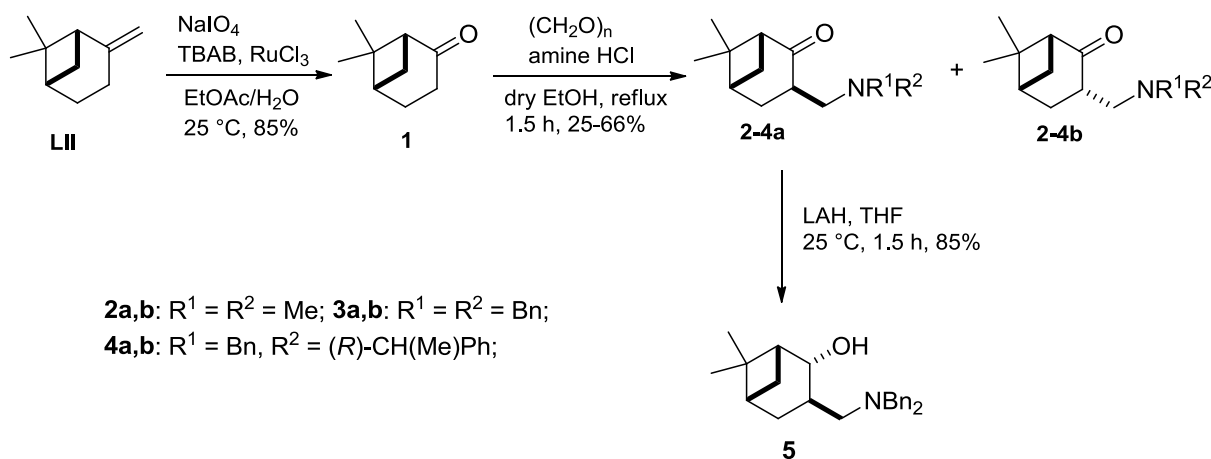
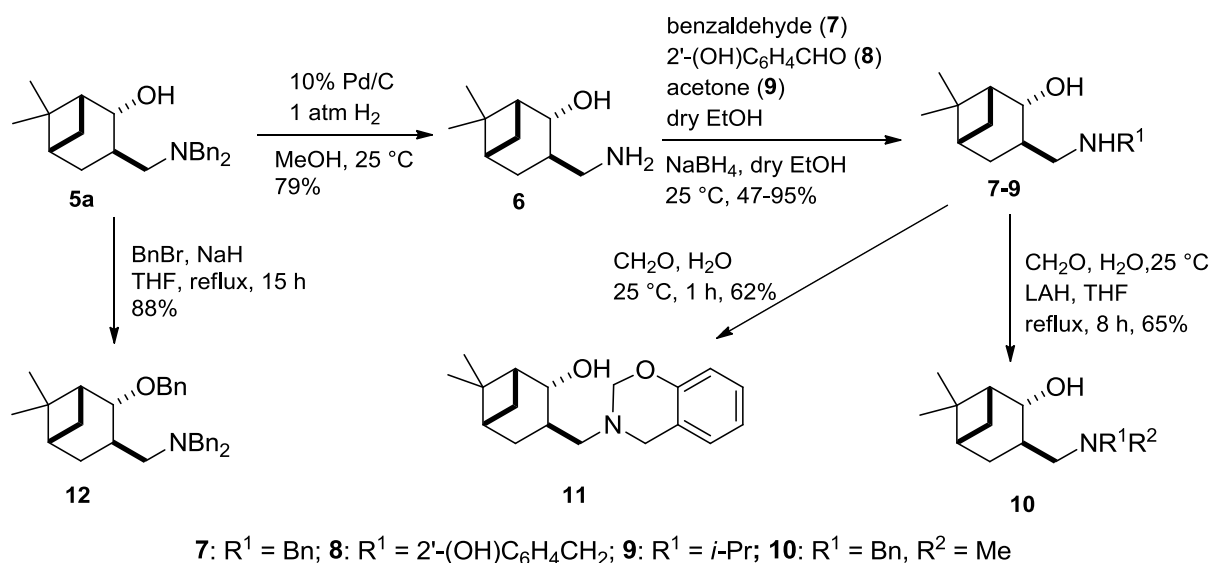


Figure 29.

Table 1. Formation of Mannich-bases **2-4**

Product	R ¹	R ²	Yield (%)	dr (a/b)
2	Me	Me	81	85:15
3	CH ₂ Ph	CH ₂ Ph	66	100:0
4	(<i>R</i>)-CH(Me)Ph	CH ₂ Ph	25	100:0

Catalytic debenzoylation with atmospheric H₂ in the presence of Pd on carbon resulted in our key intermediate primary aminoalcohol **6**. In order to gain secondary analogues reductive alkylations with benzaldehyde, salicylaldehyde and acetone were performed resulting in **7-9**. Ring closure of **8** with aqueous formaldehyde solution went regioselectively resulting in compound **11** (Figure 30). *O*-benzyl derivative **12** was also synthesized by nucleophilic substitution on the hydroxyl group.

**Figure 30.**

3.1.2 Synthesis of diols derived from (-)-β-pinene

As catalytic activity of asymmetric diols is known in the literature we also aimed to prepare monoterpene-based diols.^{124,125} Starting from nopinone (**1**) in the presence of NaH and dimethyl-carbonate β-oxoester **13** was synthesized by literature method.¹²⁶ Reduction of **13** in the presence of NaBH₄ at 0 °C proceeded with high stereoselectivity. According to NMR

measurements the ratio of the major product **14** and the minor compound **15** was 95:5. *Cis*- β -hydroxyester **14** underwent isomerisation in the presence of NaOMe affording **15** with excellent yield. Reduction of compound **14** and **15** with LiAlH₄ furnished pinane-based *cis* diol **16** and *trans* diol **17** (Figure 31).

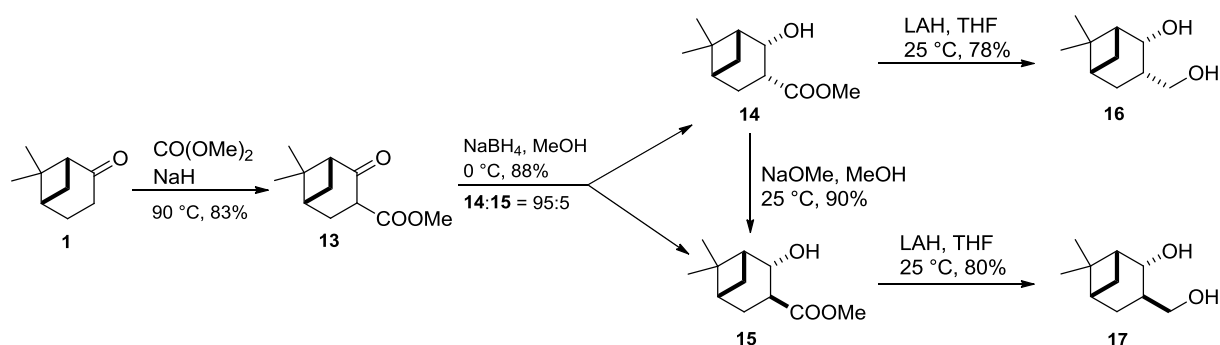


Figure 31.

Since the Mannich-condensation followed by reduction of the resulting aminoketones (**2-4**) served only *trans* 1,3-aminoalcohols we also aimed to prepare *cis* 1,3-aminoalcohol analogues starting from the β -hydroxy ester **14**. To avoid base catalysed isomerisation, hydrolysis of **14** was performed under acidic conditions while in the case of the *trans* compound (**15**) LiOH was applied resulting in **19** in a fast reaction with good yield. Amidation of **18** and **19** with DCC and benzylamine and subsequent reduction of the formed amides with LiAlH₄ resulted in *cis* 1,3-aminoalcohol **22** and its *trans* counterpart **7** which was identical with the compound obtained by an alternative reaction pathway (Figure 32).

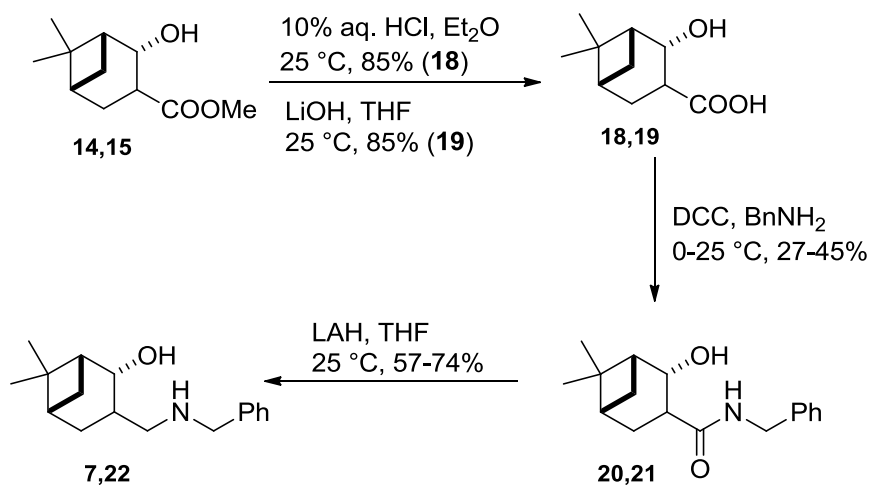


Figure 32.

3.1.3 Partial *N*-debenzylation by flow chemistry

Synthesis of compound **7** was also attempted in a H-Cube reactor. Our aim was to obtain product **7** in a one step procedure and with higher yield compared to the method presented on Figure 30.

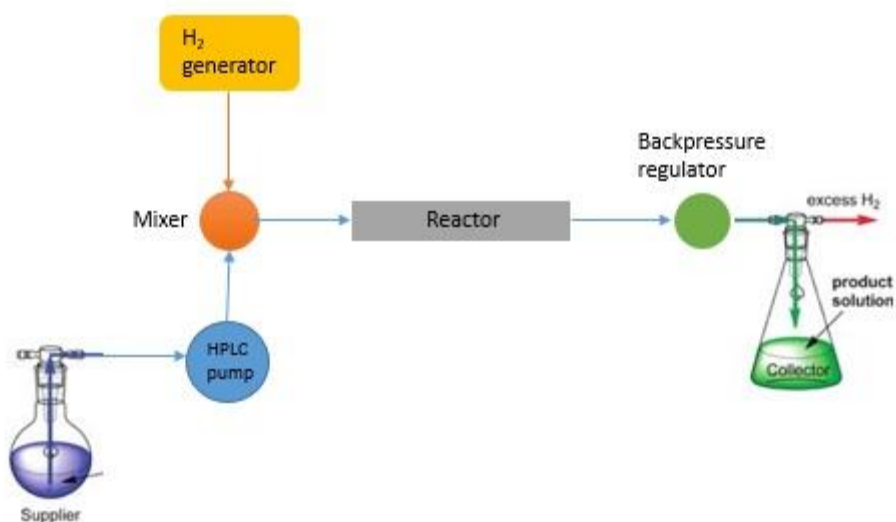


Figure 33.

As catalytic debenzylation reaction was performed in batch over Pd on carbon, that was our initial choice of catalyst. At 80 °C with a flow rate of 1 ml/min quantitative conversion was achieved – exclusively the formation of primary aminoalcohol **6** was observed. Lowering the temperature to 50 °C the desired secondary amine became detectable, while at room temperature **7** was the major product with a ratio of 81% at full conversion. Decreasing the residence time of the substrate on the catalyst bed (increasing the flow rate) resulted in a slight increase at the product ratio (85%) but at the expense of conversion (92%). Deactivation of the catalyst was also observed: after 2 h of continuous use the conversion decreased to 39%. Probably this was due to the irreversible adsorption of the substrate or the products on the charcoal. Therefore we changed the catalyst to Pd on BaSO₄. At room temperature and with a flow rate of 1 ml/min the selective formation of **7** was observed at a conversion rate of 91%. BaSO₄ as a carrier also proved to be a better choice as deactivation of the catalyst was slower, after 2 h continuous use 59% conversion was detected (Figure 34).

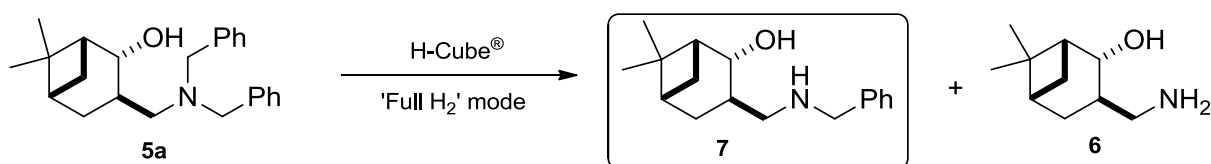


Figure 34.

Table 2. Selective debenzylation in continuous flow reactor

Catalyst	T / °C	Flow mL min ⁻¹	Conversion (%)	Selectivity (%)	
				7	6
10% Pd/C	80	1	100	0	100
10% Pd/C	50	1	100	23	77
10% Pd/C	25	1	100	81	19
10% Pd/C	25	1.5	92	85	15
10% Pd/C	25	0.5	100	73	27
5% Pd/BaSO ₄	25	1	91	100	0

3.2 Synthesis of 3-amino-1,2-diols and *O,N*-heterocycles derived from pulegone

3.2.1 Synthesis of chiral 3-amino-1,2-diols

The synthesis started from commercially available (*R*)-(+)-pulegone (purchased from Sigma Aldrich Co., *ee* = 95%, checked by GC). **23** was reduced stereoselectively to (1*R*,5*R*)-pulegole (**24**) in the presence of NaBH₄ at low temperature with excellent yield by a literature method.¹²⁷ Overman-rearrangement – since its first report in 1974 – became a powerful tool for the preparation of allylamines from allyl alcohols.^{128,129} **24** was transformed to trichloroacetimidate (**25**) applying trichloroacetonitrile in the presence of DBU as a strong base. Intermediate **25** was transformed to allylamine **26** via a heat and base (K₂CO₃) induced rearrangement (Figure 35).

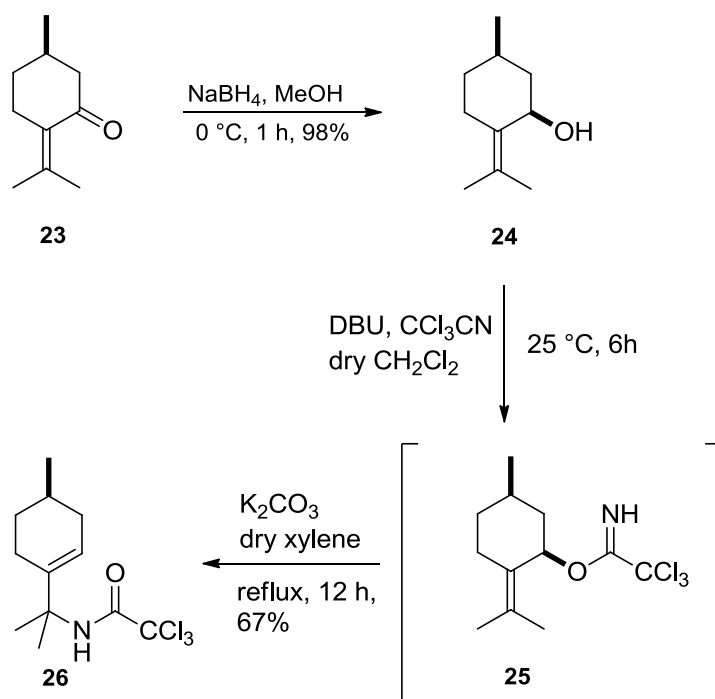


Figure 35.

In order to establish the aminodiol moiety, we planned an asymmetric dihydroxylation reaction. Our attempt, to perform the reaction in the presence of KMnO_4 failed, only mixture of diastereomers was isolated with poor yield (10%). Applying OsO_4 as catalyst and NMO as oxidant the reaction proceeded with acceptable yield (78%) but also resulting in a diastereomeric mixture (Figure 36).

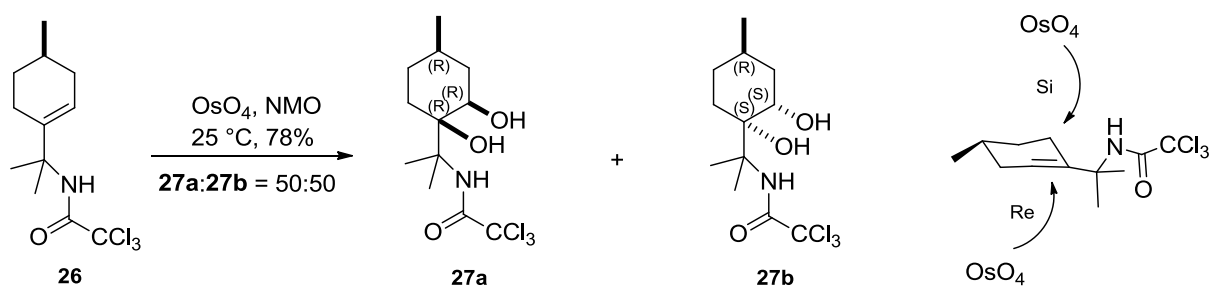


Figure 36.

According to the NMR measurements performed on the crude product, the proportion of *N*-trichloroacetyl-protected aminodiol **27a** and **27b** was found exactly 1:1. Presumably the only chiral centre in compound **26** had no chiral induction on the dihydroxylation reaction at all. In order to make the dihydroxylation reaction stereoselective, we also applied commercially available AD mix β (a mixture of 1,4-*bis*[(*S*)-[(2*R*,4*S*,5*R*)-5-ethyl-1-azabicyclo[2.2.2]octan-2-

yl]-(6-methoxyquinolin-4-yl)methoxy]phthalazine, potassium carbonate, potassium ferricyanide and potassium osmate dihydrate)¹³⁰, but the formation of the products could not be detected even after a long reaction time.

Compound **27a** and **27b** were separated by column chromatography and purified by recrystallization from *n*-hexane/EtOAc. Apart from NMR measurements, the structure of **27a** and **27b** – and also the relative configuration of the new chiral centers – were confirmed by X-ray crystallography (Figure 37).

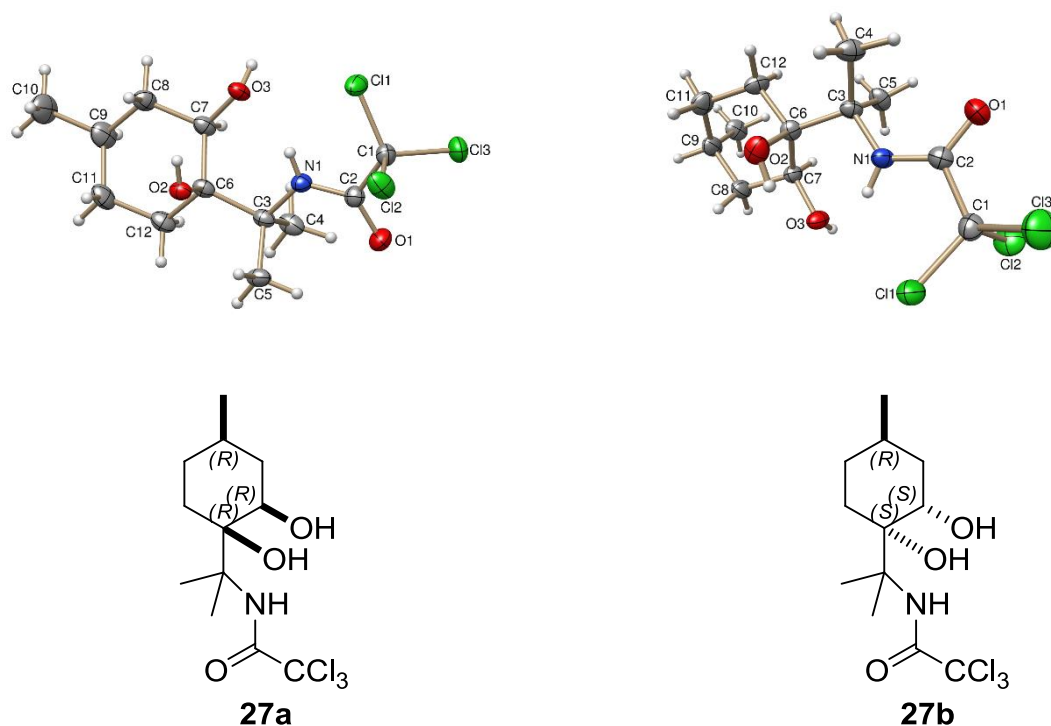


Figure 37.

Several methods are known in the literature for the removal of trichloroacetyl protecting group¹³¹⁻¹³³, in our case – despite of the long reaction time – stirring with 18% aqueous HCl provided the best yield. The obtained primary aminodiols **28a** and **28b** were transformed to secondary analogues via reductive alkylation with benzaldehyde (**29a**, **29b**). In order to increase the steric hindrance of the *N*-substituent of the proposed catalyst, we also performed reductive alkylation with 3,5-di-*tert*-butylbenzaldehyde (**30a**, **30b**) (Figure 38).

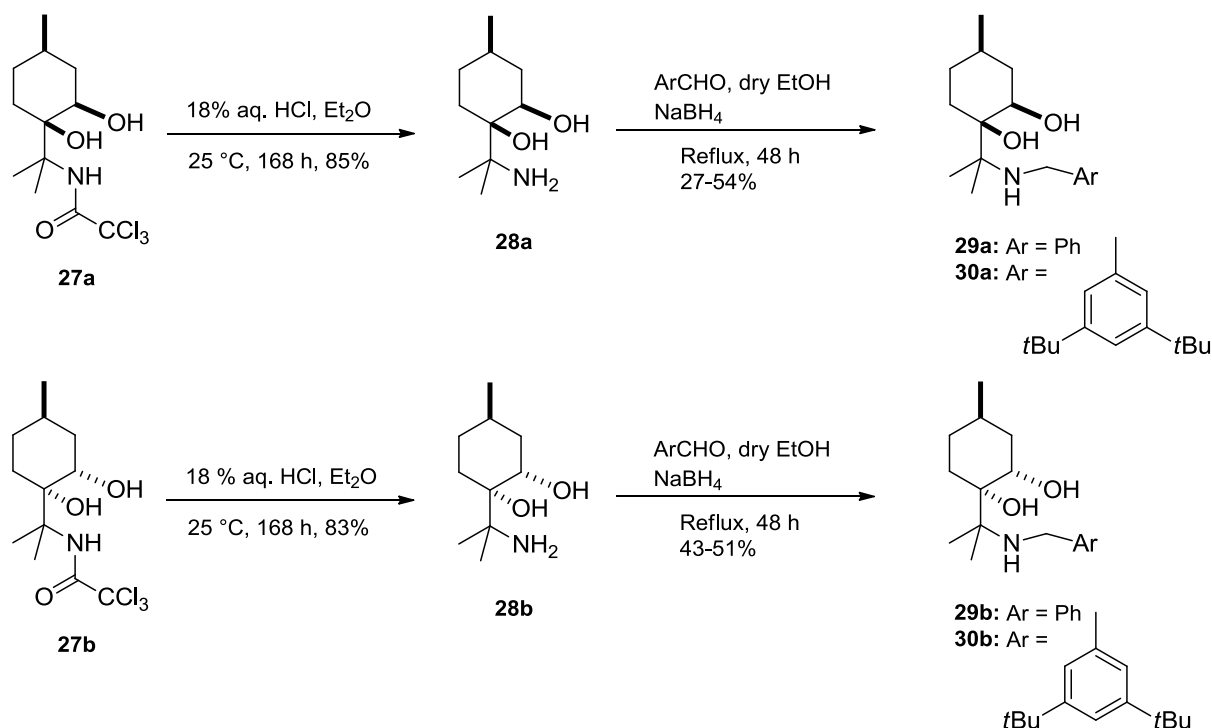


Figure 38.

3.2.2 Study on the regioselectivity of the ring closure process of pulegone-based aminodiols

As aminodiols are important starting materials of *O* and *N* containing heterocycles, we were also interested in the ring closure abilities of compounds **29a** and **29b**. Depending on which hydroxyl group takes part in the ring closure, the formation of 1,3-oxazines and oxazolidines is possible. However, in former researches, the ring closure reactions of monoterpene-based aminodiols proceeded regioselectively: in the case of carane-based aminodiol analogues the formation of carane-fused 1,3-oxazines was exclusive.^{58,62} When ring closure tendencies of pinane-based aminodiol analogues were investigated the regioselective formation of the pinane-fused or spiro-oxazolidines was both observed.^{59,66}

In our case stirring **29a** with 35% formaldehyde solution resulted in both possible products: the formation of the spiro oxazolidine and the fused oxazine ring was also detected. Although the separation of the two products was successfully accomplished the proportion of the heterocyclic products changed even in solid state in the deep freezer reaching an equilibrium mixture.

When the time dependence of the ring-closure was studied – following the reaction by the means of TLC – first only the oxazolidine product (**32a**) was detectable in the reaction mixture while after the completion of the reaction the oxazine:oxazolidine ratio was approximately 1:2

based on the ^1H NMR measurement of the crude product. The conversion between the kinetic product (oxazolidine) and the thermodynamic product (oxazine) was so fast, that even during a longer ^{13}C NMR measurement of the pure oxazolidine traces of oxazine compound was observable on the spectrum. The conversion of the mixture to the oxazine product in crystalline state was complete after 1 month while resolving the crystals resulted in isomeric mixture again. According to DFT modelling studies performed, an acid catalysed reversible interconversion takes place by protonation on the oxygen attached to the cyclohexane ring (Figure 39).

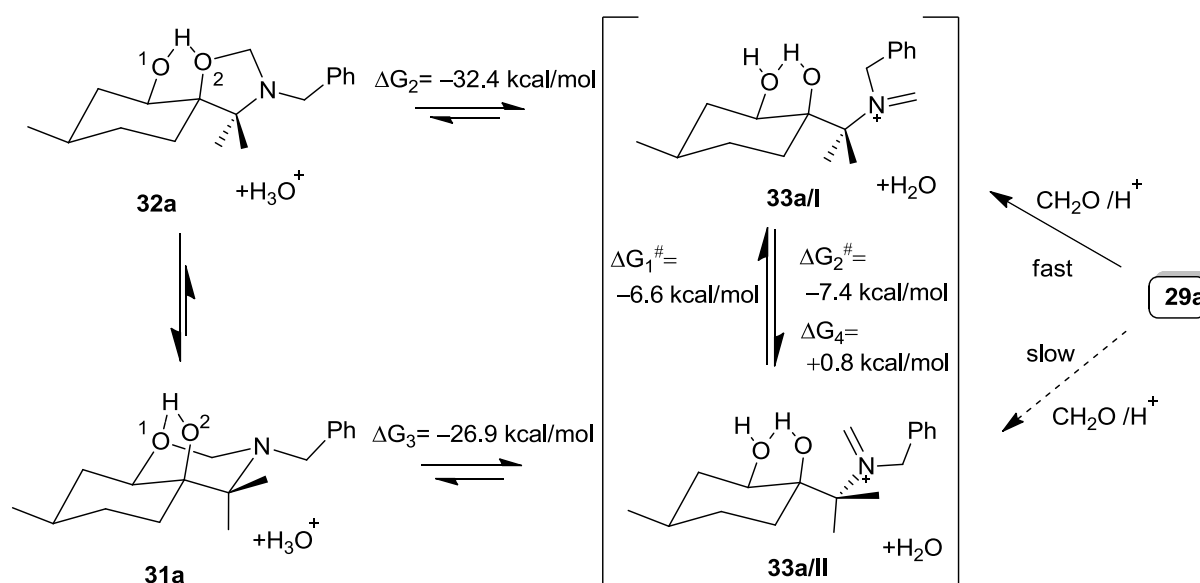


Figure 39.

The ring closure was performed with compound **29b** as well with similar results. The chemical structure of the heterocyclic products (**31a**, **32a**, **31b**, **32b**) was determined by 2D NMR measurements.

In order to gain more information on the role of the configuration of the hydroxyl groups on the catalytic activity and on the ring closure tendencies, we also planned to prepare diastereomers of the above described aminodiols. Epoxidation of **26** in the presence of MCPBA proceeded with good yield and moderate diastereoselectivity. According to NMR measurements on the crude product the proportion of the isomers was 2:1. Our attempt, to separate the diastereomers by column chromatography on silica led to the recognition that SiO_2 is acidic enough to hydrolyse the oxirane ring, resulting in our *N*-trichloroacetyl protected aminodiols (**34**) with good yield. Stirring epoxide **33** with SiO_2 in the presence of water was our method of choice

for opening the oxirane ring even on a gram scale. Compound **34a** and **34b** were separated by column chromatography. Unfortunately in this case removal of the protecting group was unsuccessful: reduction with NaBH₄ did not furnish the primary aminodiol nor acidic or strongly alkaline conditions resulted in the desired compounds (Figure 40).

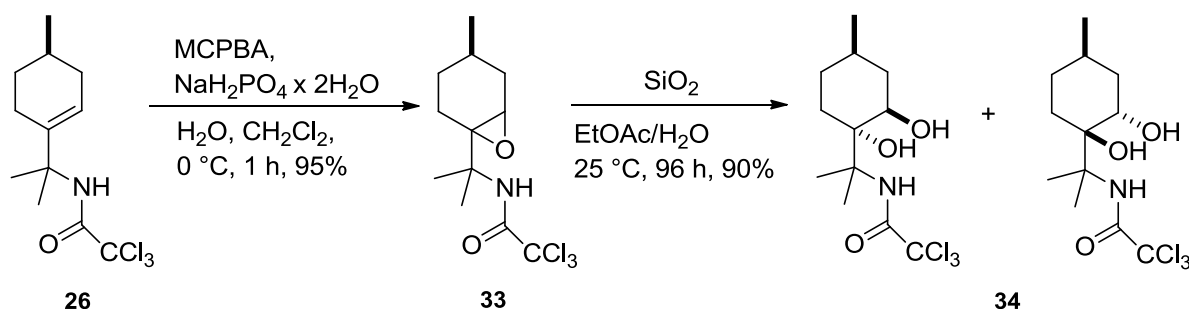


Figure 40.

3.3 Synthesis of diaminoalcohols derived from (1*R*)-(-)-myrtenol

Commercially available (1*R*)-(-)-myrtenol was stereoselectively transformed to *N*-trichloroacetyl-substituted allylamine **35** according to literature method.⁵⁹ Epoxidation of **35** in the presence of MCPBA went stereoselectively, resulting in our key intermediate epoxide **36** (Figure 41). In order to obtain the diaminoalcohol moiety, we planned the regioselective aminolysis of the oxirane ring in the presence of LiClO₄ as catalyst.

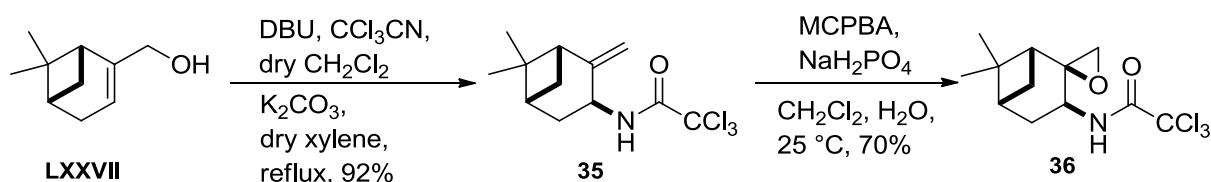


Figure 41.

Although aminolysis of **36** proceeded with high regioselectivity resulting in *N*-trichloroacetyl-protected diaminoalcohols, in certain cases – presumably via a base catalysed thermal cyclisation – the formation of oxazolidinone-type products was also detected. By increasing the temperature, the concentration and basicity of the applied amine, the formation of the tricyclic product was favoured. Standard reaction conditions were the following: the reactions were performed in dry MeCN in the presence of 4 equiv. amine and 0.1 equiv. LiClO₄ (Figure 42).

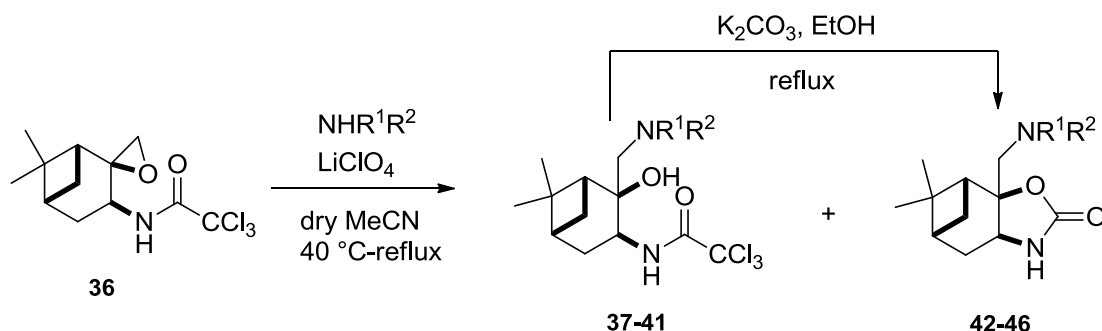


Figure 42.

In the case of dimethylamine – due to the high basicity of the amine – exclusively the oxazolidinone (**46**) product formed. When applying *R* and *S* α -methylbenzylamine the bicyclic products (**39** and **40**) were detected in the reaction mixture with low yield, while the tricyclic compounds (**44** and **45**) were the major products of the reaction at full conversion. In the case of dibenzylamine standard reaction circumstances afforded the *N*-protected diaminoalcohol **37** while with extended reaction time and in more concentrated reaction mixture the formation of oxazolidinone-type product **42** was observed exclusively. Aminolysis with benzylamine afforded the tricyclic product **43** at standard circumstances, but preparation of the bicyclic compound **38** was also possible at 40 °C in a diluted reaction mixture. In case of *N*-methyl-*N*-benzylamine the formation of product **41** was exclusive.

During the NMR studies an unexpected extreme $\delta \text{Me}_{\alpha-9}$ value (0.11 ppm) was measured for oxazolidine-2-one **42**, and the stereostructure was refined by means of DFT geometry.

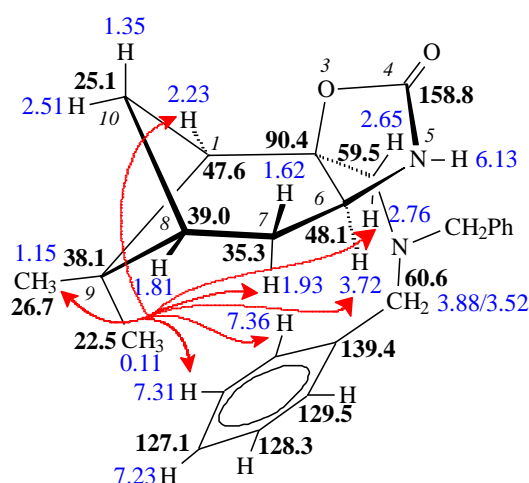


Figure 43.

Figure 43 represents the schematic stereostructure and characteristic NOESY steric proximities (red arrows) of compound **42**. Blue numbers refer to ^1H chemical shifts.

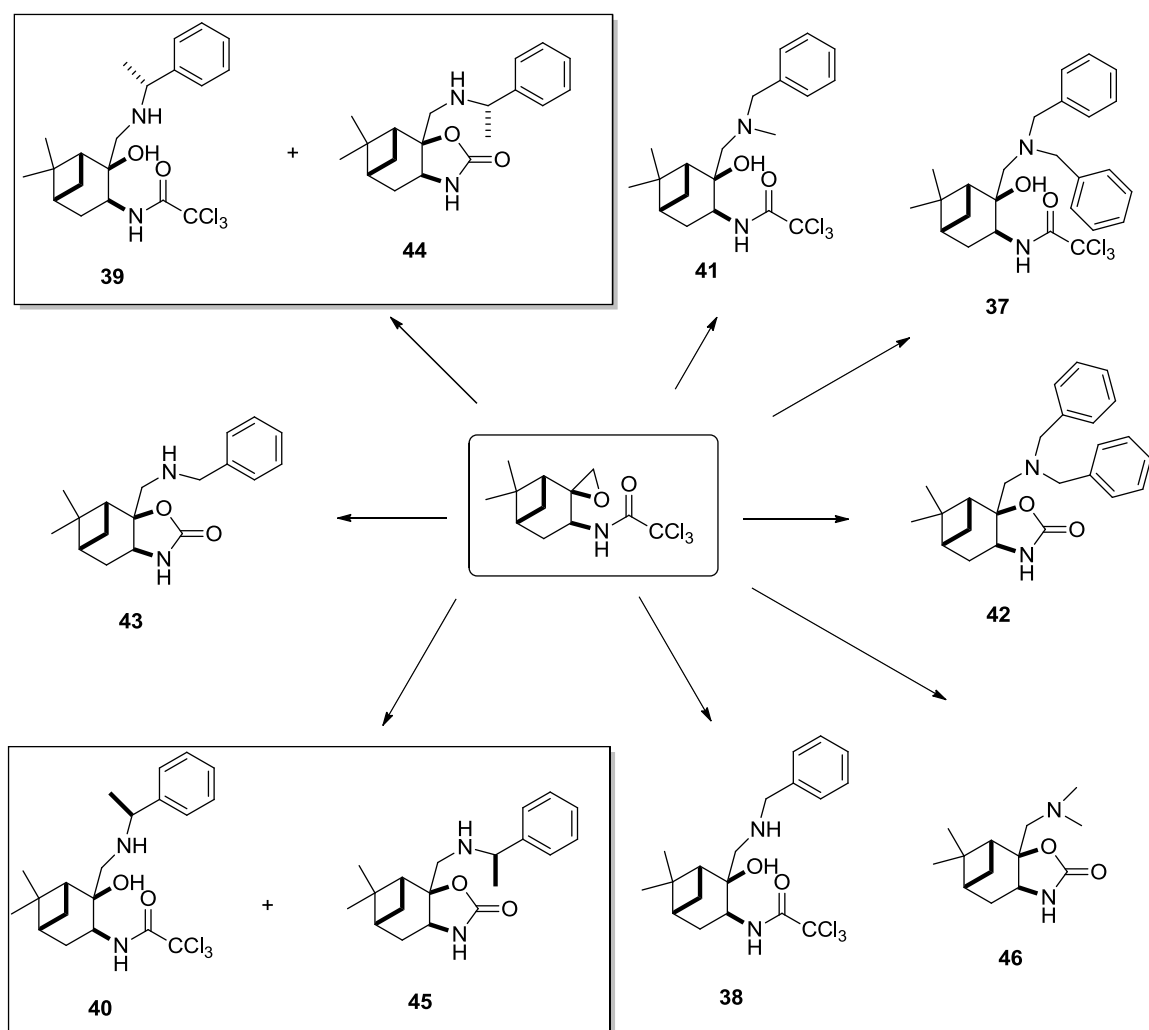


Figure 44.

Table 3. Synthesis of pinane-based diaminoalcohols and oxazolidinones

Compound	Temperature	Reaction time (h)	Yield (%)
37	reflux	20	20
42	reflux	48	66
38	40 °C	10	20
43	reflux	10	70
39	reflux	5	9
44			87
40	reflux	10	18
45			42
41	reflux	7	20
46	reflux	10	82

Our presumption – that the formation of the oxazolidinone ring is a base catalysed thermal cyclisation – was confirmed when formation of **45** from **40** was quantitative in the presence of K_2CO_3 at elevated temperature (Figure 42).

Further derivatives were prepared in order to gain more information on the effect of substitution level on the amino groups. Azidolysis of the oxirane ring was performed and similarly to the aminolyses, the reaction proceeded with high regioselectivity. Exclusively the tricyclic form was observed (**47**), presumably due to the higher temperature. The azido group was reduced to amino group by catalytic hydrogenation in the presence of Pd on carbon catalyst (Figure 45).

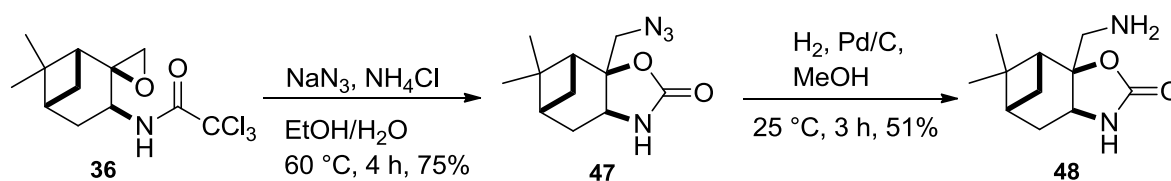


Figure 45.

Compound **43** was converted to the *N*-methyl analogue **49** in the presence of $LiAlH_4$. The benzyl group of **49** was removed with catalytic dehydrogenation, resulting in derivative **50** (Figure 46).

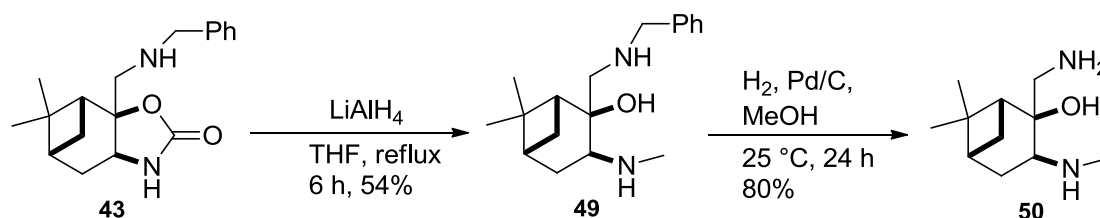


Figure 46.

As the trichloroacetyl protecting group applied for the synthesis of diaminoalcohol derivatives was again unremovable – neither $NaBH_4$, nor acidic conditions led to the unprotected targets, while utilisation of basic conditions resulted in cyclisation – a protecting group exchange was planned. Our choice of protecting group was Boc group, due to its easy cleavage. *N*-trichloroacetyl group of **35** proved to be removable under alkaline conditions, resulting in **51** with good yield. After Boc protection of allylamine **51**, epoxidation with MCPBA was performed, which – in accordance with our previous results – proceeded with high stereoselectivity. Aminolysis was performed with benzylamine and dibenzylamine furnishing compounds **54** and **55** exclusively. When the opening of the oxirane ring was accomplished

with dimethylamine, the previously prepared tricyclic analogue **46** was observed due to the high basicity of the amine.

Boc protecting group was easily removable under acidic conditions, the obtained hydrochloride salts of compounds **56** and **57** were liberated. Catalytic debenzoylation of **56** afforded analogue **58** (Figure 47).

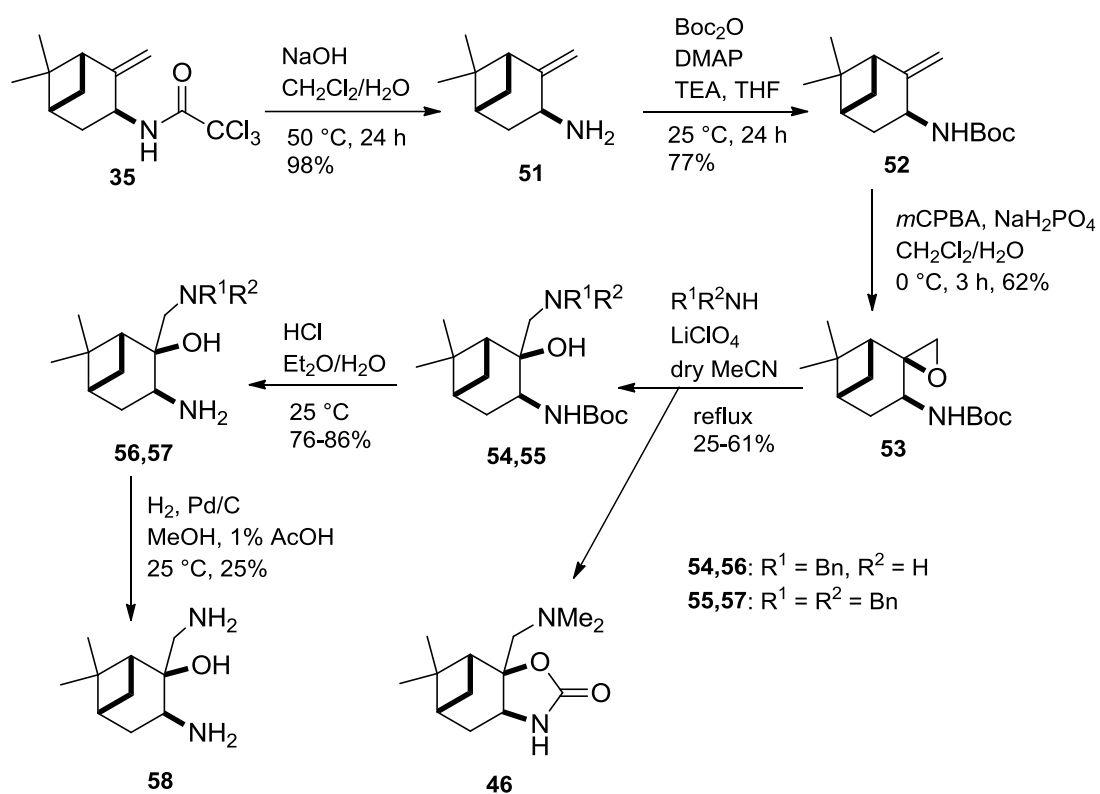


Figure 47.

4. Application of monoterpene-based chiral catalysts in the nucleophilic addition of diethylzinc to benzaldehyde

The enantioselective addition of diethylzinc to benzaldehyde is a deeply investigated model reaction in chiral catalysis as it is a powerful tool for the formation of chiral secondary alcohols.¹³⁴⁻¹³⁶ It is also widely used due to its simplicity: requires mild conditions and proceeds at room temperature under Ar atmosphere.

Structural factors, as the absolute configuration and the skeleton of the catalyst, the steric hindrance of the substituents have great influence on the transition state, therefore it greatly influences the proportion of the obtained secondary alcohols as well.

The standard reaction conditions for the model reaction are the following: commercially available solution of diethylzinc in *n*-hexane was applied and the catalysts were dissolved in this solution before the addition of benzaldehyde and applied in 10 % molar ratio. The reaction mixture was stirred for 20 h at room temperature. The proportion of the obtained 1-phenyl-1-propanols was determined by GC on CHIRASIL-DEX CB column according to literature method.^{137,138}

4.1 Application of pinane-based 1,3-aminoalcohols, 1,3-diols and their derivatives in the model reaction

The obtained aminoalcohols (**5**, **6-10**), 1,3-diols (**16**, **17**) and amides (**20**, **21**) were applied as chiral catalysts in the reaction of benzaldehyde and diethylzinc.

Although the chemical yield of the reactions was satisfactory in each case, low asymmetric catalytic activity was observed. The best *ee* value (*ee* = 26%) was observed in the case of β -hydroxyamide **21**. The low selectivity was presumably due to the disadvantageous, sterically highly hindered configuration of the hydroxyl group at position 2, so a stable transition state between the aminoalcohol and the diethylzinc could not be formed.

As low enantioselectivity was achieved in each case we also investigated the effect of the solvent and the temperature on the product ratio. Unfortunately changing the solvent to toluene and decreasing the temperature to 0 °C did not enhance the enantioselectivity.

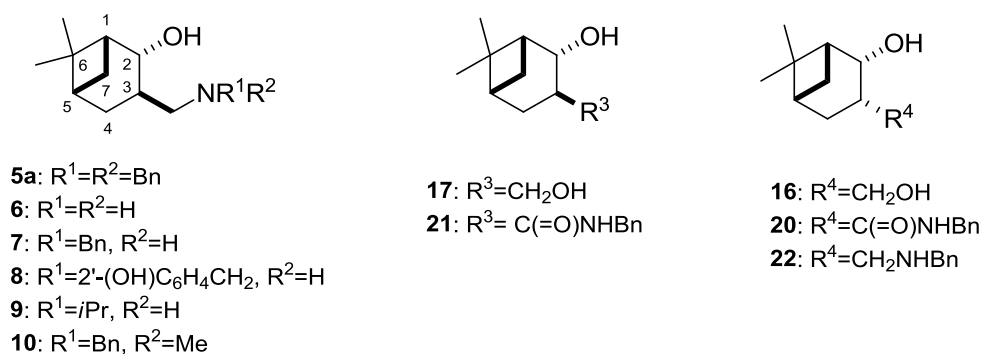


Figure 48.

Table 4. Addition of Et_2Zn to benzaldehyde catalyzed by pinane-based 1,3-aminoalcohols, β -hydroxyamides and 1,3-diols

Entry	Catalyst	Temperature	Solvent	Yield (%)	ee (%)	Config. of major product
1	5	rt	<i>n</i> -hexane	84	16	(<i>S</i>)
2	5	0 °C	<i>n</i> -hexane	82	8	(<i>S</i>)
3	5	rt	toluene	85	3	(<i>R</i>)
4	5	0 °C	toluene	80	4	(<i>R</i>)
5	6	rt	<i>n</i> -hexane	78	14	(<i>S</i>)
6	7	rt	<i>n</i> -hexane	87	13	(<i>S</i>)
7	8	rt	<i>n</i> -hexane	82	9	(<i>R</i>)
8	9	rt	<i>n</i> -hexane	86	6	(<i>R</i>)
9	10	rt	<i>n</i> -hexane	81	2	(<i>S</i>)
10	11	rt	<i>n</i> -hexane	83	6	(<i>S</i>)
11	12	rt	<i>n</i> -hexane	86	8	(<i>S</i>)
12	16	rt	<i>n</i> -hexane	86	13	(<i>S</i>)
13	17	rt	<i>n</i> -hexane	88	14	(<i>S</i>)
14	20	rt	<i>n</i> -hexane	80	18	(<i>S</i>)
15	21	rt	<i>n</i> -hexane	81	26	(<i>S</i>)
15	21	rt	toluene	80	16	(<i>S</i>)
17	22	rt	<i>n</i> -hexane	74	4	(<i>S</i>)

4.2 Application of aminodiols derived from pulegone in the model reaction

The obtained pulegone-based aminodiols were applied in the reaction of benzaldehyde and diethylzinc at standard reaction conditions. In the case of primer aminodiol **28a** low enantioselectivity was observed, while its stereoisomer **28b** showed absolutely no chiral induction in the model reaction resulting in racemic mixture of 1-phenyl-1-propanols. When *N*-benzyl-substituted aminodiols **29a** and **29b** were used as chiral catalysts moderate selectivity was observed, while increasing steric hindrance on the aromatic group did not imply enhanced selectivity.

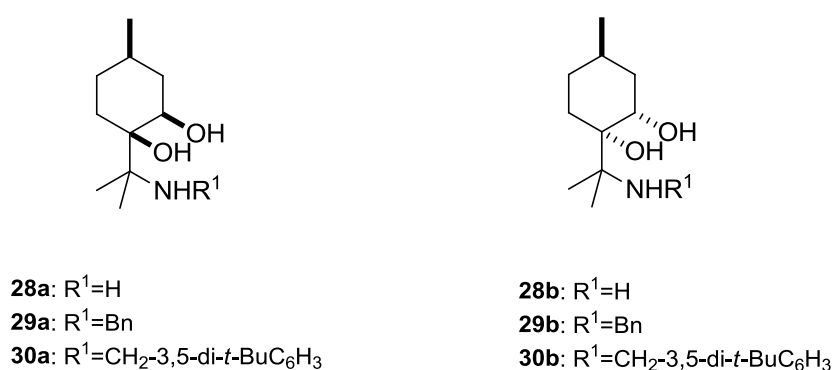


Figure 49.

Table 5. Addition of Et₂Zn to benzaldehyde catalyzed by 3-amino-1,2-diols derived from pulegone

Entry	Catalyst	Yield (%)	<i>ee</i> (%)	Config. of major product
1	28a	87	28	(<i>S</i>)
2	28b	85	0	-
3	29a	75	67	(<i>R</i>)
4	29b	89	36	(<i>S</i>)
5	30a	87	12	(<i>R</i>)
6	30b	85	54	(<i>S</i>)

4.3 Application of *O,N*-heterocycles derived from pulegone in the model reaction

Applying the obtained oxazines **31a**, **31b** and oxazolidine **32b** in the model reaction resulted in moderate enantioselectivity while in the case **32a** good selectivity ($ee = 90\%$) was measured. Interestingly ring closure of **29a** switched enantioselectivity from *R* to *S* which can be explained with a different transition state in the catalytic reaction.

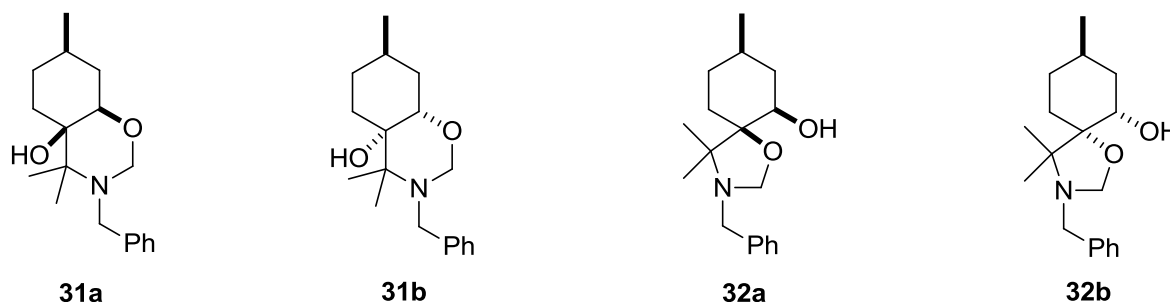


Figure 50.

Table 6. Addition of Et_2Zn to benzaldehyde catalyzed by *O,N*-heterocycles derived from pulegone

Entry	Catalyst	Yield (%)	<i>ee</i> (%)	Config. of major product
1	31a	88	64	(<i>R</i>)
2	31b	83	46	(<i>S</i>)
3	32a	90	90	(<i>S</i>)
4	32b	87	44	(<i>S</i>)

The results obtained clearly show that the (1*R*,2*R*,4*R*)-diastereomers have higher catalytic activities compared with (1*S*,2*S*,4*R*)-ones. As the interconversion between the oxazolidines and oxazines is fast, freshly prepared compounds were used in the catalytic reaction.

4.4 Application of pinane-based diaminoalcohols and oxazolidinones in the model reaction

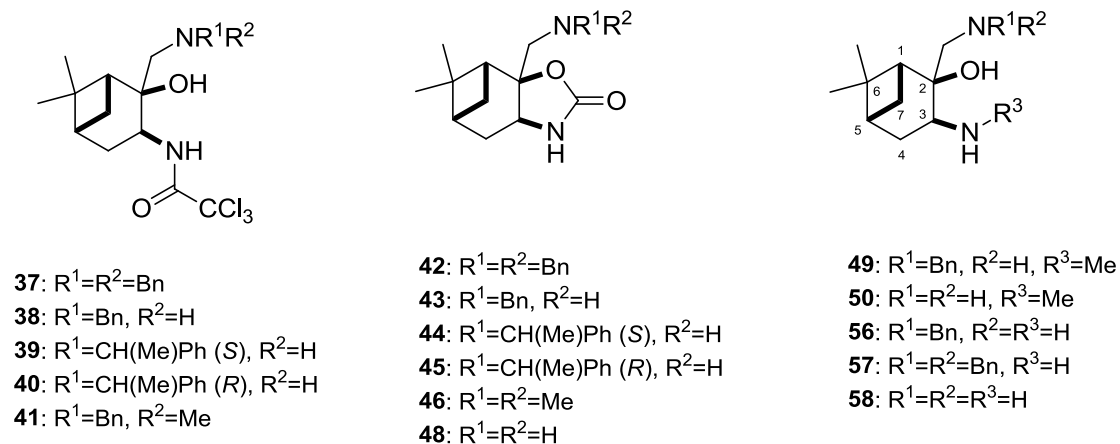


Figure 51.

The synthesized pinane-based *N*-protected diaminoalcohols (**37-41**), oxazolidinones (**42-46**, **48**) and tridentate diaminoalcohols (**49,50, 56-58**) were applied in the model reaction.

In the case of *N*-trichloroacetyl-diaminoalcohols very low selectivity was observed while when applying the oxazolidinone analogues the enantioselectivity slightly increased except for the azido compound which expressed no selectivity, resulting in racemic enantiomer mixture. Tridentate ligand **49** and **50** showed low chiral induction whereas in the case of compound **56** and **57** moderate selectivity was observed. Presumably coordination to the primary amino group at position 3 seems to be crucial for the formation of a stable transition state in the catalytic reaction. Whereas, varying the size of the substituents on the aminomethyl group induced no significant change in the enantioinduction but in the case of primary aminomethyl group at position 2 a significant decrease was observed in enantioselectivity (Figure 51).

Table 7. Addition of Et₂Zn to benzaldehyde catalyzed by pinane-based diaminoalcohols

Entry	Catalyst	Yield (%)	<i>ee</i> (%)	Config. of major product
1	37	85	4	<i>S</i>
2	38	88	2	<i>R</i>
3	39	79	0	-
4	40	89	8	<i>S</i>
5	41	79	6	<i>S</i>
6	42	85	24	<i>S</i>
7	43	90	24	<i>S</i>
8	44	84	24	<i>R</i>
9	45	84	24	<i>R</i>
10	46	88	2	<i>S</i>
11	47	83	0	-
12	48	87	18	<i>R</i>
13	49	77	34	<i>R</i>
14	50	88	18	<i>R</i>
15	56	87	74	<i>S</i>
16	57	85	72	<i>S</i>
17	58	88	8	<i>S</i>

5. Summary

Bi- and trifunctional monoterpene-based chiral compound libraries have been prepared via stereoselective synthesis. During the course of the experimental work 52 new, structurally diverse compounds have been synthesised and characterized.

Starting from commercially available (-)- β -pinene nopinone was prepared from which aminoketons have been obtained via Mannich-condensation with secondary amines. In the case of dibenzylamine the reaction proceeded with high diastereoselectivity. Reduction of **3** resulted in pinane-based aminoalcohol in a stereoselective manner. Catalytic debenzylation served primary aminoalcohol whose reductive alkylation reactions with various aldehydes resulted in secondary derivatives. Reaction of **7** with formaldehyde yielded *N*-benzyl-*N*-methyl analogue, while nucleophilic substitution on the hydroxyl group resulted in the *O*-benzyl analogue.

Starting from nopinone the synthesis of pinane-based oxoester was also performed. Subsequent reduction of the keto group resulted in β -hydroxyesters in a highly diastereoselective transformation. Reaction of **14** and **15** resulted in pinane-based diols, while hydrolysis afforded β -hydroxy-carboxylic acids. Amidation in the presence of DCC yielded amides. Reduction of amides with LiAlH_4 afforded *cis*-*N*-benzyl aminoalcohol **22** and its previously prepared *trans* counterpart **7** via a different synthetic strategy.

The *trans*-*N*-benzyl-1,3-aminoalcohol (**7**) was synthesised by a third route as well. Exploiting the advantages of flow chemistry a selective method has also been developed for the synthesis of **7** by the catalytic hydrogenation of aminoalcohol **5**.

Transformation of pulegone by a well known literature method resulted in pulegole. Overman rearrangement of allylic alcohol **24** resulted in the formation of allylic amine **26**. Dihydroxylation of the unsaturated bond afforded diastereomers: *N*-trichloroacetyl protected aminodiols in an exactly equal proportion. Removal of the protecting groups resulted in primer aminodiols while reductive alkylations resulted in secondary derivatives.

Ring closure abilities of **29a** and **29b** was also investigated in the presence of formaldehyde, both the formation of spiro-oxazolidine and the ring fused oxazine was detected. Moreover, an acid-catalyzed reversible interconversion – a ring-ring tautomerism – can take place between the two isomers: the oxazolidine is the kinetic product of the reaction, while the oxazine is the more stable thermodynamic product.

Simple synthetic procedures have been developed for the stereoselective synthesis of pinane-based diaminoalcohols: starting from commercially available (1*R*)-myrtenol key

intermediate epoxyamine **36** was prepared in two-steps. Aminolysis and azidolysis proceeded regioselectively resulting in variously substituted *N*-trichloroacetyl diaminoalcohols and via a base catalysed thermal cyclization reaction the formation of pinane-ring fused oxazolidinones was also observed.

As the trichloroacetyl protecting group of the prepared diaminoalcohol proved to be unremovable, an alternative synthesis route via Boc protection has been developed for the preparation of target molecules.

The prepared optically active 1,3-aminoalcohols, diols, 3-amino-1,2-diols and their oxazine and oxazolidine derivatives, the prepared *N*-trichloroacetyl protected diaminoalcohols, the unprotected analogues and oxazolidinones were applied as chiral catalysts in the asymmetric addition of diethylzinc to benzaldehyde. The pinane-based 1,3-aminoalcohols showed poor selectivity (up to *ee* = 26%). Presumably the low catalytic activity observed was due to the high steric hindrance of the *endo* hydroxy group at position 2, caused by the dimethylmethylene bridge of the pinane ring system. Similarly, the chiral induction of the pinane-based oxazolidinones proved to be weak (up to *ee* = 24%). The tridentate ligands as pinane-based diaminoalcohols and aminodiols derived from pulegone exerted weak to moderate enantioselectivity (up to *ee* = 74%), while applying heterocycles prepared from 3-amino-1,2-diols in the model reaction in the case of compound **32a** resulted in good enantioselectivity (*ee* = 90%).

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Scientific lectures

Gonda Tímea, Szakonyi Zsolt, Fülöp Ferenc

Monoterpénvázas királis 1,3-aminoalkoholok előállítása, átalakításai és alkalmazása királis katalizátorként

XXXVII. Kémiai Előadói Napok

Szeged, November 3-5, 2014, oral presentation

Tímea Gonda, Zsolt Szakonyi, Ferenc Fülöp

Stereoselective synthesis and application of tridentate aminodiols derived from pulegone

16th Tetrahedron Symposium

Berlin, June 16-19, 2015, P1.075, poster presentation

Gonda Tímea, Szakonyi Zsolt, Fülöp Ferenc

(*R*)-(+)-Pulegonból származtatható monoterpénvázas aminodiolok és 1,3-heterociklusok sztereoszelektív előállítása és alkalmazása

MTA Szteroid- és Terpenoidkémiai Munkabizottság és az MTA Szegedi Akadémiai Bizottság Szerves és Gyógyszerkémiai Munkabizottsági Ülés

Szeged, October 12, 2015, oral presentation

Gonda Tímea, Szakonyi Zsolt, Csámpai Antal, Fülöp Ferenc

Királis aminodiolok és diaminoalkoholok sztereoszelektív előállítása és átalakításai

Heterociklusos és Elemorganikus Kémiai Munkabizottsági Ülés

Balatonszemes, May 18-20, 2016, oral presentation

Tímea Gonda, Zsolt Szakonyi, Ferenc Fülöp

Synthesis and application of tridentate diaminoalcohols derived from (1*R*)-(-)-myrtenol

Chirality 2016

Heidelberg, Germany, July 24-27, 2016, P20, poster presentation

Tímea Gonda, Zsolt Szakonyi, Ferenc Fülöp

Monoterpénvázas diaminoalkoholok előállítása és alkalmazása királis katalizátorként

Pillich Lajos Miniszimpózium

Budapest, Richter Gedeon NyRT, February 15, 2017, oral presentation

Zsolt Szakonyi, **Tímea Gonda**, Péter Bérdi, István Zupkó, Ferenc Fülöp

Stereoselective synthesis, synthetic and pharmacological application of monoterpene-based 1,2,4- and 1,3,4-oxadiazoles

17th Blue Danube Symposium on Heterocyclic Chemistry

Linz, Austria, August 30 – September 2, 2017, poster presentation

Publication list

- [1] Zsolt Szakonyi, **Tímea Gonda**, Sándor Balázs Ötvös, Ferenc Fülöp
Stereoselective synthesis and transformations of chiral 1,3-aminoalcohols and 1,3-diols derived from nopinone
Tetrahedron: Asymmetry, **2014**, 25, 1138-1145
- [2] **Tímea Gonda**, Zsolt Szakonyi, Antal Csámpai, Matti Haukka, Ferenc Fülöp
Stereoselective synthesis and application of tridentate aminodiols derived from (+)-pulegone
Tetrahedron: Asymmetry, **2016**, 27, 480-486
- [3] **Tímea Gonda**, Attila Balázs, Gábor Tóth, Ferenc Fülöp, Zsolt Szakonyi
Stereoselective synthesis and transformations of pinane-based 1,3-diaminoalcohols
Tetrahedron, **2017**, 73, 2638-2648