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

Summary of PhD thesis

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Szeged

2017

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. 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. 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. 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. 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.

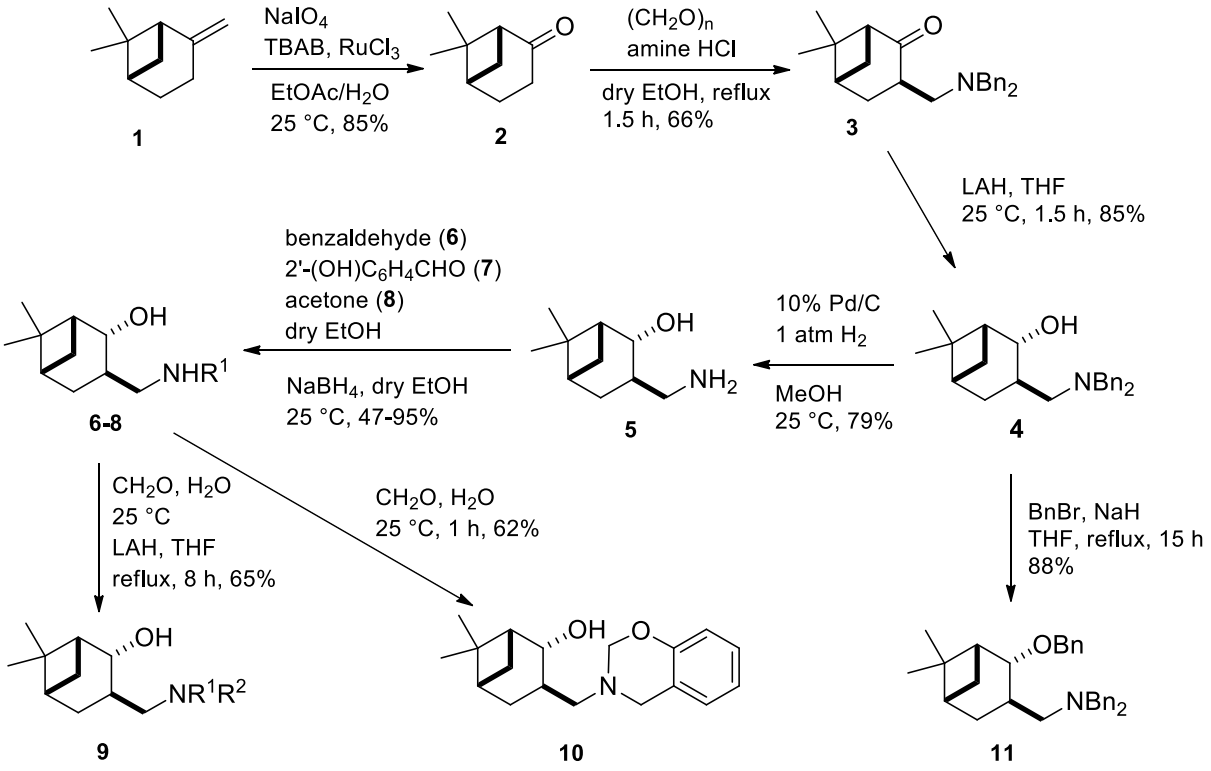
Applied investigation methods

Reactions were performed on a mmol scale, and products were separated and purified by silica gel column chromatography or by recrystallization. All new compounds were characterized by their melting points, NMR, elemental analysis and optical rotations. Enantiomeric excess of 1-phenyl-1-propanols was checked by chiral stationary-phase GC. Complex structures were identified by means of two-dimensional NMR techniques (COSY, HSQC, HMBC and NOESY) and X-ray crystallography.

Results and discussion

1. Synthesis of pinane-based 1,3-aminoalcohols

Novel enantiopure 1,3-aminoalcohols have been synthesized starting from commercially available β-pinene according to Scheme 1. Mannich condensation of nopinone with dibenzylamine hydrochloride proceeded with high stereoselectivity as well as the subsequent reduction of keto group. Further modifications of key product **4** resulted in an aminoalcohol compound library (**5-11**).

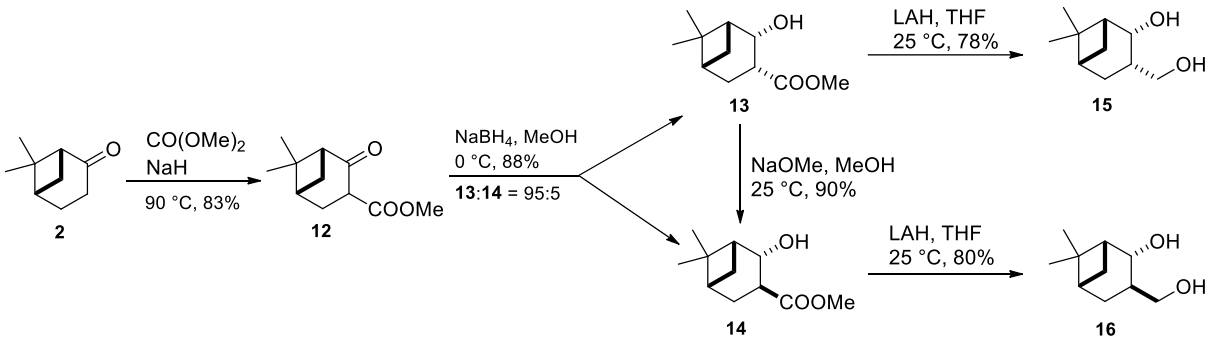


6: R^1 = Bn; **7**: R^1 = 2'-(OH)$C_6H_4CH_2$; **8**: R^1 = *i*-Pr; **9**: R^1 = Bn, R^2 = Me

Scheme 1.

2. Synthesis of pinane-based 1,3-diols

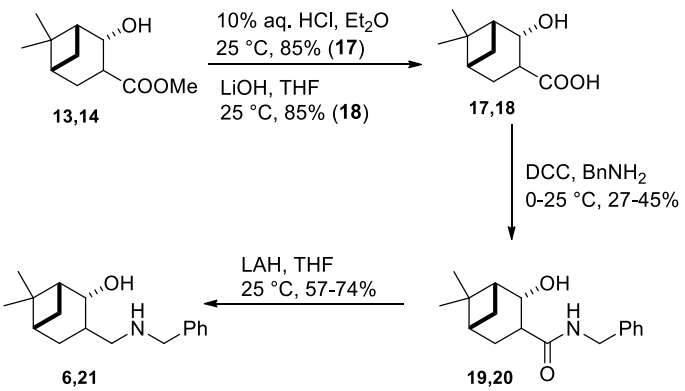
Starting from nopinone (**2**) in the presence of NaH and dimethylcarbonate β-oxoesther **12** was synthetized. Subsequent reduction with $NaBH_4$ proceeded with high diastereoselectivity resulting in *cis* β-hydroxyesther **13** and its *trans* counterpart (**14**) as minor product. Reduction with $LiAlH_4$ furnished pinane-based 1,3-diols **15** and **16** (Scheme 2).



Scheme 2.

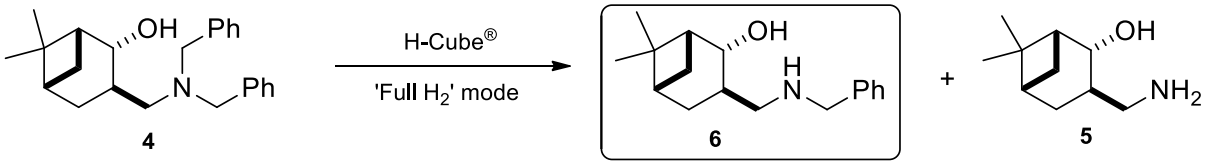
3. Alternative synthesis pathways of pinane-based *N*-benzyl-aminoalcohol (6)

Since the Mannich-condensation followed by reduction of the resulting aminoketone served only *trans* 1,3-aminoalcohols we also aimed to prepare *cis* analogues starting from the β-hydroxy ester **13**. To avoid base catalysed isomerisation, hydrolysis of **13** was performed under acidic conditions while in the case of the *trans* compound (**14**) LiOH was applied resulting in **18** in a fast reaction with good yield. Amidation of **17** and **18** with DCC and benzylamine and subsequent reduction of the formed amides with $LiAlH_4$ resulted in *cis* 1,3-aminoalcohol **21** and its *trans* counterpart **6** which was identical with the compound obtained by an alternative reaction pathway (Scheme 3).



Scheme 3.

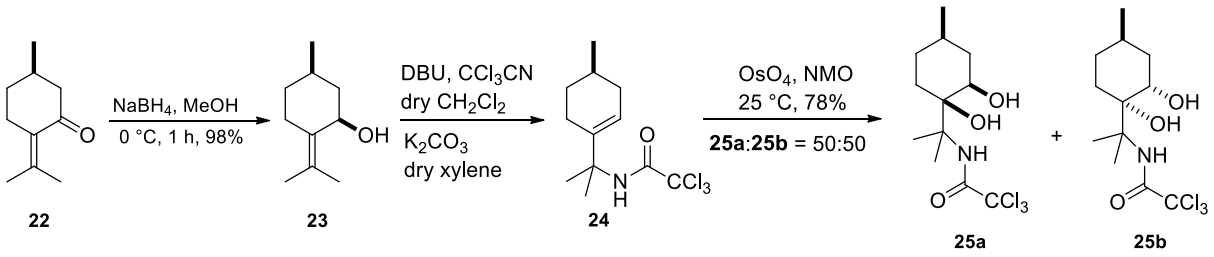
Selective synthesis of **6** was also performed in a H-Cube® reactor with catalytic debenzylation over Pd/C and Pd on $BaSO_4$ (Scheme 4). The temperature, the flow rate and the pressure was optimized in order to increase the yield.



Scheme 4.

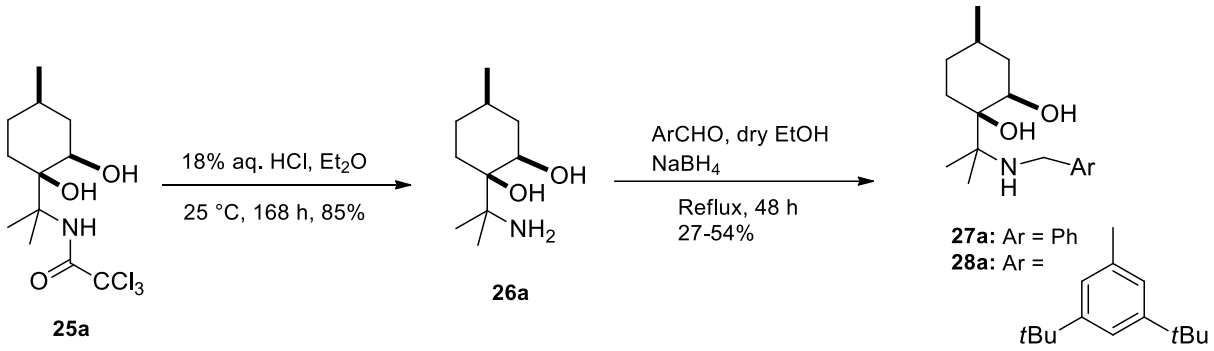
4. Synthesis of tridentate aminodiols from (*R*)-pulegone

Pulegole (**23**) was synthesized from commercially available (*R*)-(+)-pulegone (**22**). Allylic alcohol **23** was transformed into trichloroacetyl-protected allylamine **24** via Overman-rearrangement. In order to establish the protected aminodiol moiety OsO_4 catalysed *syn*-dihydroxylation was performed. According to NMR measurements on the crude product the ratio of the resulting **25a** and **25b** diastereomers was exactly 1:1 (Scheme 5). The relative configuration of the obtained products (**25a** and **25b**) was determined applying 2D NMR techniques and X-ray crystallography.



Scheme 5.

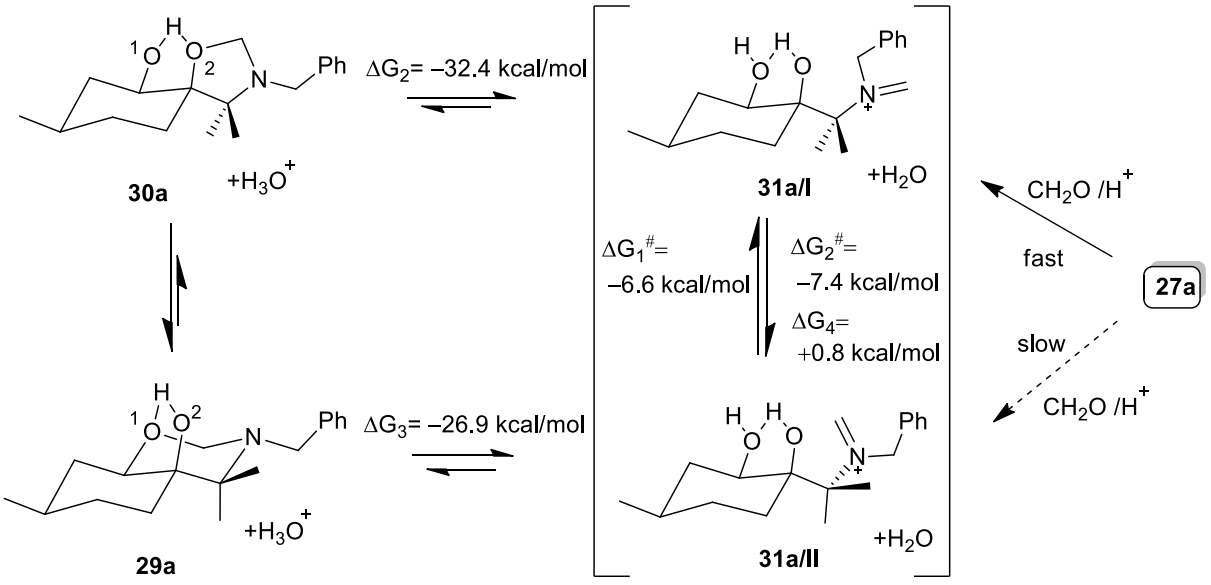
Trichloroacetyl protecting group was removed with aqueous HCl solution and the resulting primary aminodiol **26a** was transformed into secondary analogues with reductive alkylation (Scheme 6).



Scheme 6.

5. Investigation of ring-closure abilities of pulegone-based aminodiols

Ring-closure abilities of compound **27a** was also investigated. Depending on which hydroxyl group takes part in the ring closure, the formation of 1,3-oxazines and oxazolidines is possible. In our case strirring **27a** with 35% formaldehyde solution resulted in both possible products: the formation of the spiro oxazolidine and the fused 1,3-oxazine ring was also detected. According to DFT modelling studies performed, an acid catalysed reversible interconversion takes place by protonation on the oxygen attached to the cyclohexane ring (Scheme 7).

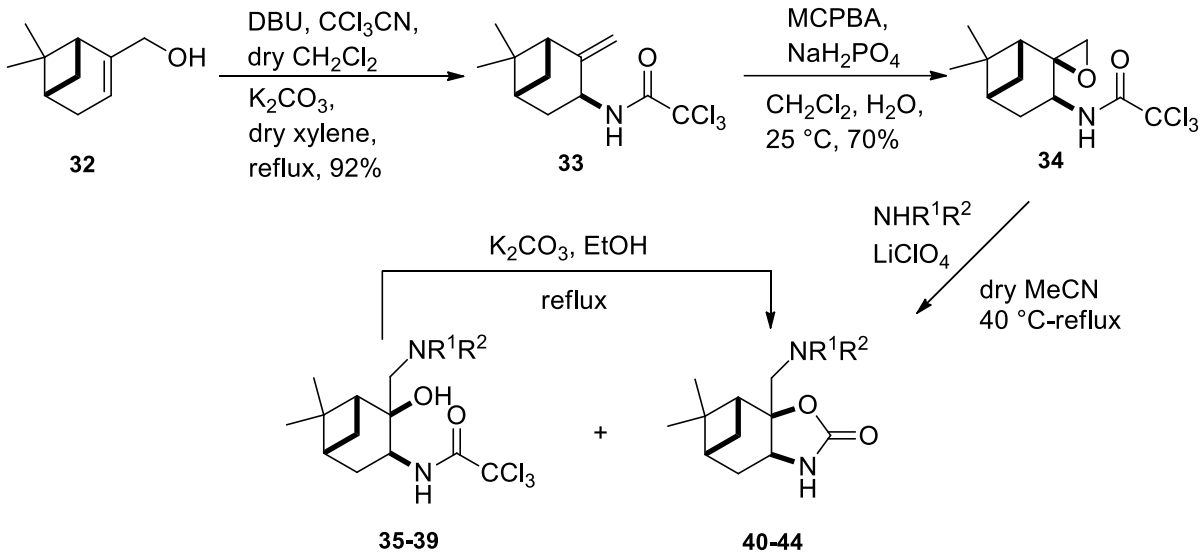


Scheme 7.

6. Synthesis of pinane-based diaminoalcohols and oxazolidinones

Commercially available (1*R*)-(-)-myrtenol was stereoselectively transformed to *N*-trichloroacetyl-substituted allylamine **33** according to literature method. Epoxidation of **33** in

the presence of MCPBA went stereoselectively, resulting in our key intermedier epoxide **34**. In order to obtain the diaminoalcohol moiety, regioselective aminolysis of the oxirane ring was performed in the presence of $LiClO_4$ as catalyst (Scheme 8).

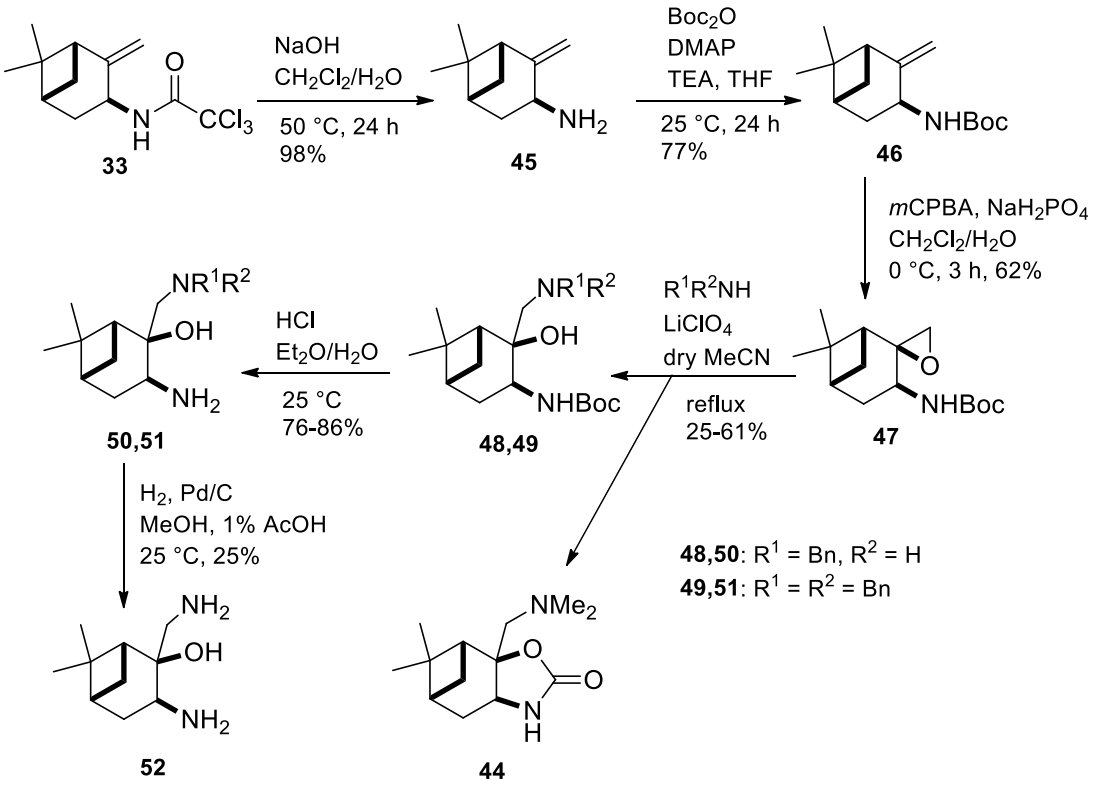


Scheme 8.

Although aminolysis of **34** 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.

As the trichloroacetyl protecting group applied for the synthesis of diaminoalcohol derivatives was unremovable, a protecting group exchange was planned. Our choice of protecting group was Boc group, due to its easy cleavage. *N*-trichloroacetyl group of **33** proved to be removable under alkaline conditions, resulting in **45** with good yield. After Boc protection of allylamine **45**, 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 **48** and **49** exclusively. When the opening of the oxirane ring was accomplished with dimethylamine, the previously prepared tricyclic analogue **44** was observed due to the high basicity of the amine.

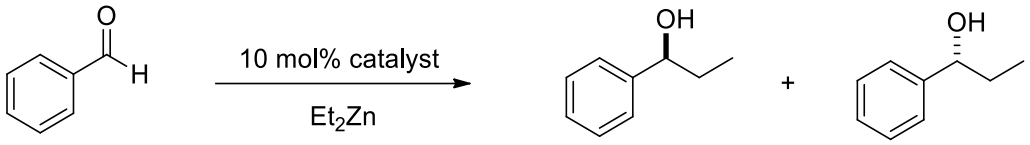
Boc protecting group was easily removable under acidic conditions, the obtained hydrochloride salts of compounds **50** and **51** were liberated. Catalytic debenzylation of **50** afforded analogue **52** (Scheme 9).



Scheme 9.

7. Application of monoterpene-based bi- and tridentate ligands as chiral catalysts in the model reaction

The prepared optically active monoterpene-based 1,3-aminoalcohols, 1,3-diols, aminodiols, monoterpene-condensed heterocycles, diaminoalcohols were applied as catalysts in the asymmetric addition of Et_2Zn to benzaldehyde (Scheme 10).



Scheme 10.

Pinane-based 1,3-aminoalcohols (**5-11**) and diols (**15** and **16**) exerted low catalytic activity in the addition of diethylzinc to benzaldehyde resulting in *R* and *S* 1-phenyl-1-propanols. The low selectivity was presumably due to the disadvantegous, 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.

Aminodiols derived from (*R*)-pulegone provided moderate enantioselectivity (up to *ee* = 67%) in the model reaction while their heterocyclic derivatives (the ring-fused oxazines and spiro-oxazolidines) exerted good enantioselectivity (up to *ee* = 90%).

Applying pinane-based diaminoalcohols and their derivatives in the model reaction resulted in low to good enantioselectivity (up to *ee* = 74%). In the case of *N*-trichloroacetyl-diaminoalcohols very low selectivity was observed while when applying the oxazolidinone analogues the enantioselectivity slightly increased. In the case of compound **50** and **51** moderate selectivity was observed. Presumably coordination to the primary amino group at position 3 seems to be crutial 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.

Conclusions

During the course of the experimental work more than 50 new compounds have been synthesized, purified and characterized starting from commercially available monoterpenes. The prepared compounds were tested as chiral catalysts in the nucleophilic addition of diethylzinc to benzaldehyde.

Publications related to the thesis

[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

IF: 2.155

[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

IF: 2.126

[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

IF: 2.651*

Other publication

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

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

International Journal of Molecular Sciences, **2018**, *19*, 81-92

IF: 3.226*

Total impact factor: 10.158

*2016 impact factors

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