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Stereoselective synthesis of monoterpene-based 1,3-diamines and 3-amino-1,2-diols and their application in enantioselective transformations

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Introduction and aims

In the past decade, considerable progress has been made in the synthesis of chiral synthons finding application as starting materials in asymmetric transformations or in enantiomerically pure form as auxiliaries and chiral ligands in enantioselective syntheses. A large majority of these compounds are derived from readily available natural products.

In asymmetric syntheses the growing need for new chiral ligands requires new strategies to obtain the desired enantiopure catalysts. One of the ways to achieve this aim is the incorporation of chirality into ligands by using naturally-occurring optically active monoterpenes as starting materials. Monoterpenes are optically active compounds that are readily available for this purpose. Besides their commercial availability, the advantage of these molecules is that the existing chiral centers will be retained in the new molecules formed, and chirality transfer generally occurs with high stereoselectivity. Moreover, bicyclic monoterpenes possess highly constrained skeletons and these rigid structures may influence the asymmetric induction. Monoterpenes such as α- and β-pinene, camphor or pulegone are excellent starting materials in asymmetric synthesis because their stereocenters mainly remain intact in further transformations and influence the configurations of newly generated stereocenters. The use of monoterpenes as chiral pools in stereoselective syntheses provides an opportunity to develop efficient synthetic methodology for the preparation of enantio-enriched optically active compounds.

The most frequently applied approach to optically active monoterpene derivatives is the transformation of the ring C-C double bond. This general mode provides an opportunity to access alicyclic β-amino acids, as valuable precursors for alicyclic 1,3-amino alcohols, diamines and aminodiols.

Besides the pharmacological importance of β-amino acids and 1,3-aminoalcohols, some natural aminodiols also exhibit marked biological activity (*e.g.* aristeromycin), while others may serve as starting materials for the synthesis of biologically active natural compounds (*e.g.* cytoxazone). Compounds containing amino carboxamide and diamine structural elements have proven antitumor or antiviral activity.

Aminodiols and diamines are also widely used as chiral auxiliaries or chiral ligands in enantioselective syntheses. The asymmetric alkylation of aldehydes by organozinc compounds has become a highly investigated C-C bond-forming reaction. It results in optically active secondary alcohols, catalyzed by chiral promoters such as 1,2- and 1,3-bifunctionalized ligands. Additionally, aminodiols are known to be excellent building blocks

for the synthesis of noteworthy heterocyclic compounds. The formation of these heterocycles depends upon which hydroxy group undergoes ring closure with the amino group.

In view of the advantages of monoterpenes, our aim was to synthetize monoterpene-based 2- or 3-functionalized building blocks such as β-amino acid derivatives or aminodiols, starting from enantiopure natural monoterpenes such as (-)-myrtenol, (-)-myrtenal and (+)-3-carene.

We also set out to develop a simple synthetic route for the preparation of various monoterpene derivatives such as aminodiols and diamines, including ring-closed ones, and to apply these bi- and trifunctionalized chiral catalysts in the enantioselective addition of Et_2Zn to various aldehydes.

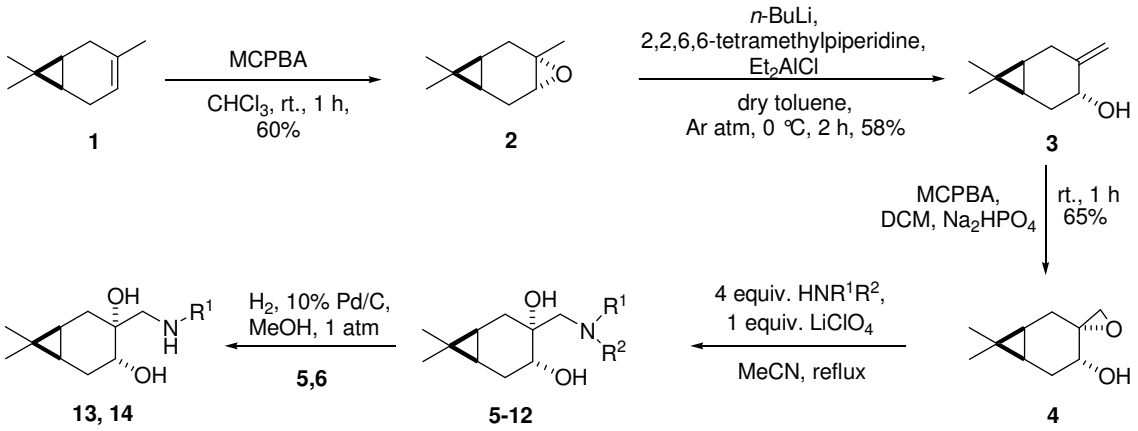
Applied investigation methods

Reactions were performed on a mmol scale, and products were separated and purified by silica gel column chromatography or by recrystallization. The newly prepared compounds were characterized by their melting points, IR, NMR and mass spectroscopy and elemental analysis. The *ee* values of enantiomers were determined by chiral stationary-phase GC and HPLC. The stereochemistry of the compounds was identified by means of two-dimensional NMR spectroscopy (COSY, HSQC, HMBC and NOESY).

Results and discussion

1. Synthesis of carane-based bifunctionalized tridentate ligands

Functionalization of enantiomeric (1*S*)-(+)-3-carene **1** was achieved by applying simple synthetic steps, including stereoselective transformations. Novel, optically active epoxy alcohol **4** was subjected to a stereoselective epoxide ring-opening procedure, resulting in variously substituted carane-based aminodiols **5**-**14** (Scheme 1).

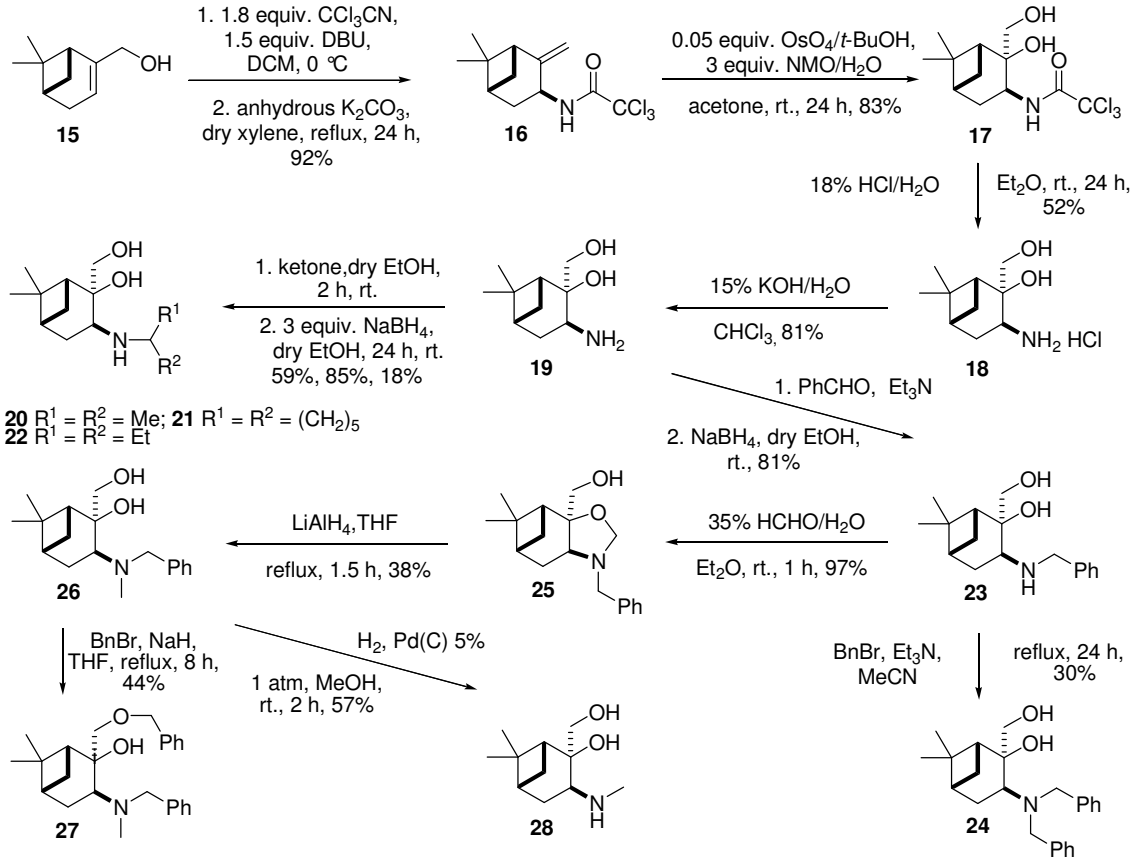


5: R^1 = Me, R^2 = CH_2Ph; **6**: R^1 = R^2 = CH_2Ph; **7**: R^1 = H, R^2 = CH_2Ph; **8**: R^1 = CH_2Ph, R^2 = CH(Me)Ph (*R*); **9**: R^1 = CH_2Ph, R^2 = CH(Me)Ph (*S*); **10**: R^1 = H, R^2 = CH(Me)Ph (*R*); **11**: R^1 = H, R^2 = CH(Me)Ph (*S*); **12**: R^1 = H, R^2 = *i*-Pr; **13**: R^1 = Me; **14:** R^1 = H

Scheme 1

2. Synthesis of pinane-based bifunctionalized tridentate ligands

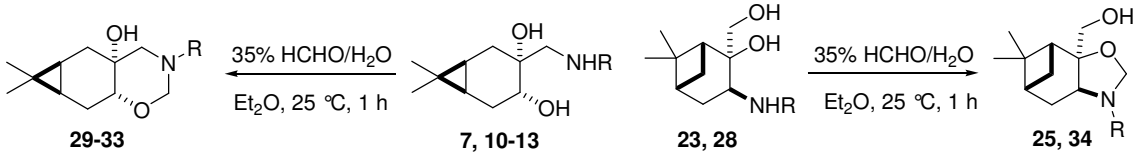
The rearrangement of readily available (1*R*)-(-)-myrtenol **15** to allylic amine **16**, followed by a dihydroxylation procedure and cleavage of the trichloroacetamide group, led to the formation of enantiopure key intermediates **18** and **19**. Through simple synthetic steps, precursors **18** or **19** were transformed to optically active pinane-based aminodiols **20**-**28** (Scheme 2).



Scheme 2

3. Synthesis of carane- and pinane-fused heterocycles

With a 35% aqueous solution of formaldehyde as a convenient cyclization agent in both reaction pathways, the regioselective ring-closure of pinane- and carane-based aminodiols furnished exclusively carane-fused 1,3-oxazines **29**-**33** and pinane-fused oxazolidines **25** and **34** (Scheme 3).

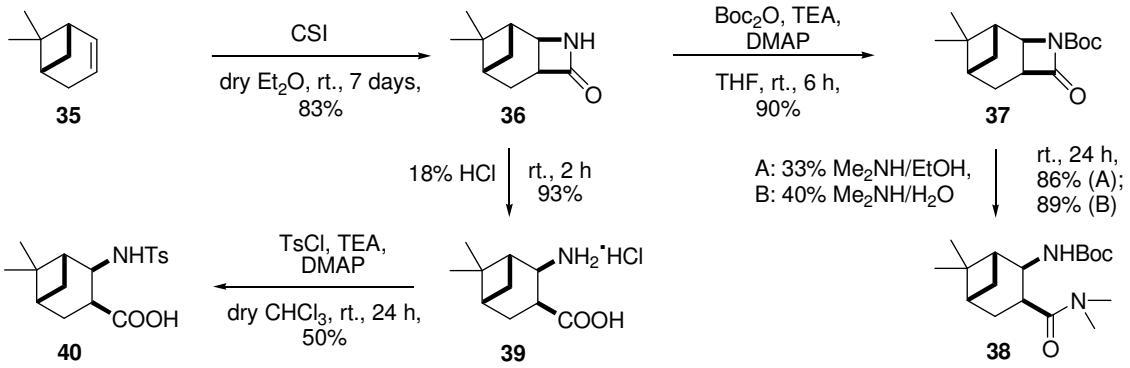


Scheme 3

4. Synthesis of pinane-based bifunctionalized bidentate ligands

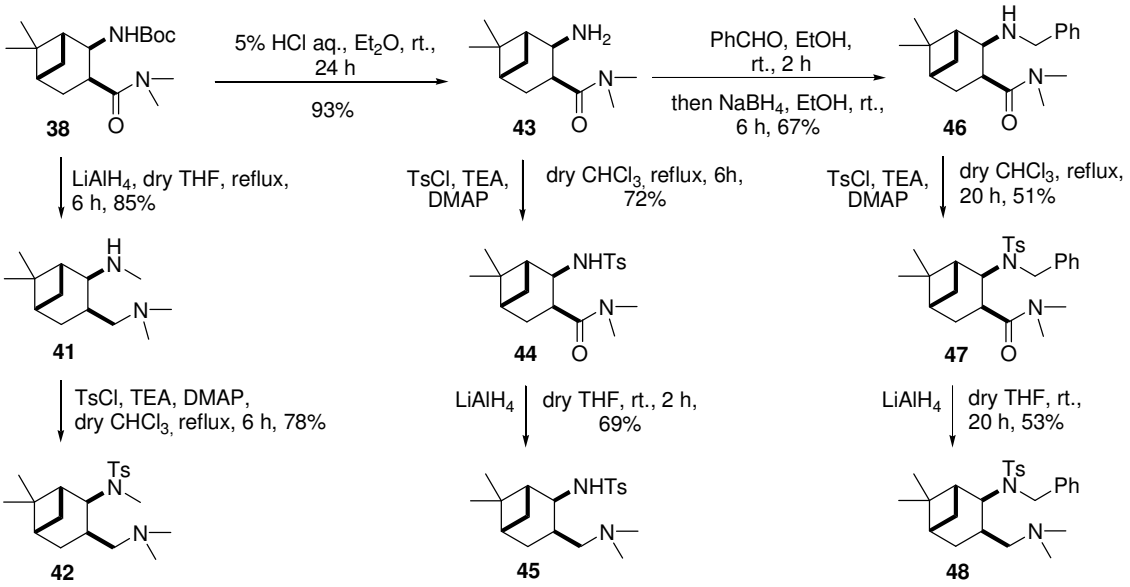
Simple synthetic procedures for the synthesis of enantiomerically pure pinane-based β-lactams **36** and the Boc-protected **37** involved regio- and stereoselective CSI addition to

enantiopure apopinene **35**. The optically active β-amino amides and 1,3-diamines were derived from **36** and **37**.



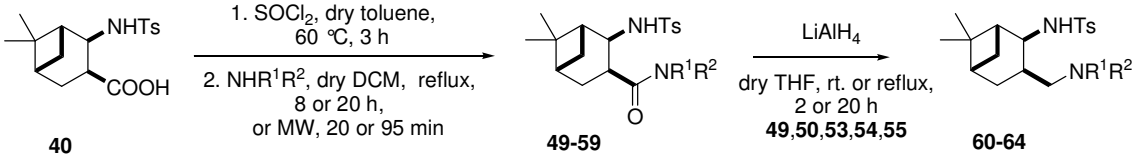
Scheme 4

The consecutive lactam-opening procedure and tosylation reaction furnished amino amides **44**, **47** and **49**-**59**.



Scheme 5

By subsequent reduction, only diamines bearing a tertiary amino function **42**, **45**, **48** and **60**-**64** could be synthetized, and hence a series of variously substituted β-amino acid derivatives were prepared.



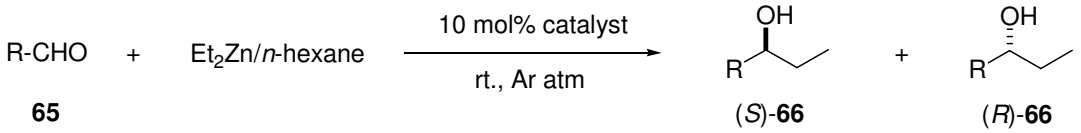
40 **49-59** **49**,**50**,**53**,**54**,**55** **60-64**

49 and **60** : R^1 = H, R^2 = R^3 = Et; **50** and **61** : R^1 = H, R^2R^3 = $(CH_2)_4$; **51**: R^1 = R^2 = H, R^3 = CH_2Ph; **52**: R^1 = R^2 = R^3 = H; **53** and **62**: R^1 = H, R^2 = Me, R^3 = CH_2Ph; **54** and **63**: R^1 = H, R^2 = Me, R^3 = Ph; **55**: R^1 = R^2 = H, R^3 = CH(Me)Ph (*R*); **56**: R^1 = R^2 = H, R^3 = CH(Me)Ph (*S*); **57**: R^1 = R^2 = H, R^3 = Me; **58** and **64**: R^1 = H, R^2R^3 = $(CH_2)_5$; **59**: R^1 = R^2 = H, R^3 = Ph

Scheme 6

5. Application of bi- and tridentate ligands as chiral catalysts in enantioselective transformations

Optically active monoterpene-based tri- and bidentate ligands and monoterpene-condensed heterocycles were applied as catalysts in the asymmetric addition of Et_2Zn to benzaldehyde. The general applicability of the catalysts and the influence of structural factors on the catalytic activity were studied.



65 (*S*)-**66** (*R*)-**66**

R = Ph or 4-$MeOC_6H_4$; 4-MeC_6H_4; 3-$MeOC_6H_4$; 3-MeC_6H_4; 2-naphthyl; cyclohexyl; *n*-butyl

Scheme 7

Carane-based tridentate catalysts **5**-**14** exerted low enantioinduction in the asymmetric addition of Et_2Zn to benzaldehyde, affording the *R* or the *S* enantiomer of 1-phenyl-1-propanol **66**. A moderate *ee* value (*ee* = 37%) was achieved by utilizing *N*-(*S*)-1-phenylethyl derivative **11**.

In comparison, improved catalytic activity was observed with pinane-based tridentate ligands **19**-**24** and **26**-**28**, yielding (*R*)-**66**. The *N*-benzyl aminodiol **23** furnished the best *ee* value (*ee* = 61%) in the test reaction. The quantum chemical molecular modeling studies performed correlated well with our experimental findings. Increasing enantioinduction was observed in the sequence NH_2 < NRR < NHR.

Carane-condensed 1,3-oxazines **29**-**33** proved to be excellent catalysts in the addition of Et_2Zn to benzaldehyde, furnishing (*S*)-**66** with high *ee* values (up to 96%). The best carane-based tricyclic catalyst was (*R*)-1-phenylethyl-substituted oxazine **31**.

In contrast, pinane-fused oxazolidines **25** and **34** displayed low chiral induction, with the formation of (*R*)-**66** as the major enantiomer.

The pinane-based bidentate ligands **42**, **44**, **45**, **47**, **48** and **49**-**64** provided moderate to good asymmetric induction in model reactions. Depending upon the degree of *N*-substitution of the β-amino acid derivatives, switching of the enantioselectivity was observed. With β-amino amides containing a primary or tertiary amide group **44**, **47**, **49**, **50**, **52**-**54** and **56** and 1,3-diamines **42**, **45**, **48** and **60**-**64**, moderate *ee* values were achieved, giving (*R*)-**66** as the major product. β-Amino amides with a secondary amide function **51**, **55**-**57** and **59** improved the enatioselectivity, providing (*S*)-**66**. The highest *ee* value (*ee* = 83%) was observed for β-amino amide **59**.

To the best of our knowledge, this is the first use of β-amino amides as suitable catalysts in the addition of Et_2Zn to benzaldehyde.

The efficiency of carane-fused 1,3-oxazine **31** (Scheme 7) was tested in an extended model reaction, giving both high yields and enantioselectivities up to 97% *ee* with *S* selectivity.

6. In the course of the experimental work, more than 50, structurally diverse monoterpene-based enantiopure aminodiols, alicyclic-condensed heterocycles and β-amino acid derivatives were prepared and characterized.

Publications related to the thesis:

[1] Zsolt Szakonyi, **Kinga Csillag**, Ferenc Fülöp:
Stereoselective synthesis of carane-based aminodiols as chiral ligands for the catalytic addition of diethylzinc to aldehydes
Tetrahedron: Asymmetry, **2011**, *22*, 1021-1027

IF: 2.652

[2] **Kinga Csillag**, Lukács Németh, Tamás A. Martinek, Zsolt Szakonyi, Ferenc Fülöp:
Stereoselective synthesis of pinane-type tridentate aminodiols and their application in the enantioselective addition of diethylzinc to benzaldehyde
Tetrahedron: Asymmetry, **2012**, *23*, 144-150

IF: 2.115

[3] **Kinga Csillag**, Zsolt Szakonyi, Ferenc Fülöp:
Stereoselective syntheses of pinane-based 1,3-diamines and their application as chiral ligands in the enantioselective addition of diethylzinc to benzaldehyde
Tetrahedron: Asymmetry, **2013**, *24*, 553-561

IF: 2.115*

[4] **Csillag Kinga**, Szakonyi Zsolt, Fülöp Ferenc:
Monoterpénvázas 1,2- és 1,3-difunkciós vegyületek sztereoszelektív szintézise és alkalmazása
Magyar Kémikusok Lapja, **2013**, *LXVIII*, 293-296

Total impact factor: 6.882

Other publications

[5] Katalin Gulácsi, István Németh, Ádám Szappanos, **Kinga Csillag**, Tünde Z. Illyés, Tibor Kurtán, Sándor Antus:
Heck-oxyarylation of 2-phenyl-2H-chromene and 1,2-dihydronaphthalene
Croatica Chemica Acta, **2013**, *86*, 137-141

IF: 0.614*

*2012 impact factor

Presentations related to the thesis

1. **Kinga Csillag**, Zsolt Szakonyi, Tamás A. Martinek, Dávid Lukács, Ferenc Fülöp:
   Carene-based aminodiols and 1,3-oxazines as ligands for the enantioselective synthesis of chiral secondary alcohols
   FOLDAMERS: Design, Synthesis and Applications
   Bologna, October 6-8, 2010, Abstr.: PS-4, p. 50, poster presentation

2. **Csillag Kinga**:
   Karánvázas aminodiolok és 1,3-oxazinok alkalmazása szekunder alkoholok enantioszelektív szintézisében
   XXXIII. Kémiai Előadói Napok
   Szeged, October 25-27, 2010, Abstr.: p. 139, oral presentation

3. **Csillag Kinga**, Szakonyi Zsolt, Fülöp Ferenc:
   Pinán- és karánvázas aminodiolok, 1,3-oxazinok és oxazolidinek sztereoszelektív előállítása és alkalmazása dietil-cink és aldehidek reakciójában
   MTA Heterociklusos Kémiai Munkabizottság Ülése
   Balatonszemes, September 26-28, 2011, oral presentation

4. **Csillag Kinga**:
   Monoterpénvázas aminodiolok sztereoszelektív szintézise és alkalmazása királis katalizátorként
   PhD subjects at the Institute of Pharmaceutical Chemistry, University of Szeged
   Szeged, February 23, 2012, oral presentation

5. **Csillag Kinga**, Szakonyi Zsolt, Fülöp Ferenc:
   Királis β-aminosav amid és 1,3-diamin származékok sztereoszelektív szintézise és alkalmazásai
   MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság Ülése
   Balatonszemes, June 5-7, 2013, oral presentation

6. **Csillag Kinga**, Szakonyi Zsolt, Fülöp Ferenc:
   Monoterpénvázas 1,3-difunkciós vegyületek sztereoszelektív szintézise és alkalmazása
   MKE Vegyészkonferencia
   Hajdúszoboszló, June 26-28, 2013, Abstr.: P-11, p. 71, poster presentation