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

PhD Thesis

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Tetrahedron: Asymmetry, **2011**, *22*, 1021-1027

[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

[3] **Kinga Csillag**, Zsolt Szakonyi, Ferenc Fülöp:
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Tetrahedron: Asymmetry, **2013**, *24*, 553-561

[4] **Csillag Kinga**, Szakonyi Zsolt, Fülöp Ferenc:
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List of abbreviations

Boc: *tert*-butoxycarbonyl

CSI: chlorosulfonyl isocyanate

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

DCM: dichloromethane

DMAP: 4-dimethylaminopyridine

DMSO: dimethyl sulfoxide

ee: enantiomeric excess

MCPBA: *m*-chloroperoxybenzoic acid

MW: microwave

NBS: *N*-bromosuccinimide

NMO: *N*-methylmorpholine *N*-oxide

PTSA: *p*-toluenesulfonic acid

rt.: room temperature

TEA: triethylamine

T_{H2}: T helper type 2

Ts: *p*-toluenesulfonyl group

TsCl: *p*-toluenesulfonyl chloride

$VO(acac)_2$: vanadyl acetylacetonate

1. 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.[1] 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.[2] Monoterpenes, such as α- and β-pinene,[3,4] camphor[5] or pulegone[6] 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.

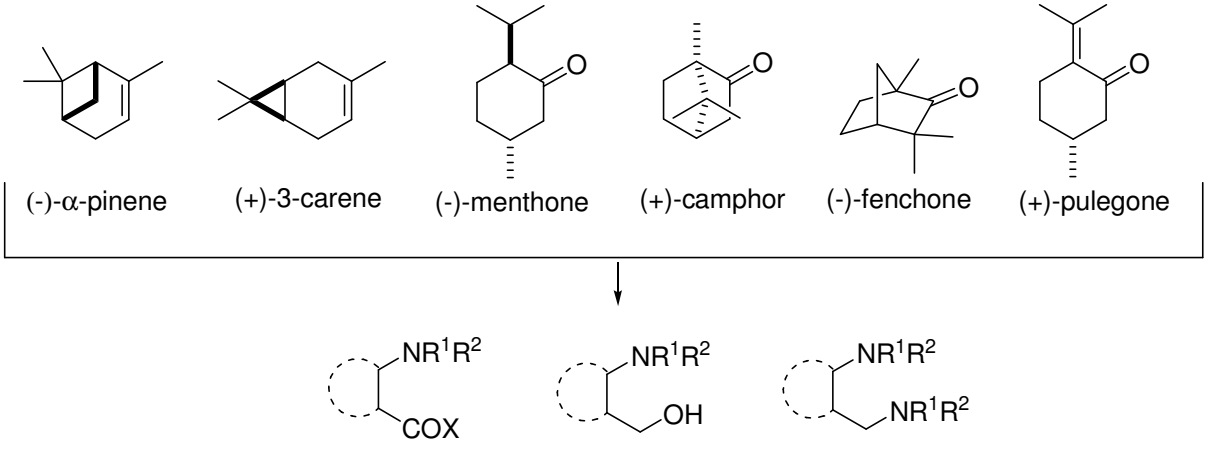


Figure 1

The most frequently applied approach to optically active monoterpene derivatives is the transformation of the ring C-C double bond.[7-11] This general mode provides an opportunity to

access alicyclic β-amino acids, as valuable precursors for alicyclic 1,3-amino alcohols, diamines and aminodiols (Figure 1).

Besides the pharmacological importance of β-amino acids and 1,3-aminoalcohols, some natural aminodiols also exhibit marked biological activity (*e.g.* aristeromycin),[12] while others may serve as starting materials for the synthesis of biologically active natural compounds (*e.g.* cytoxazone).[13] Compounds containing amino carboxamide and diamine structural elements have a proven antitumor or antiviral activity.[14-17]

Aminodiols and diamines are also widely used as chiral auxiliaries or chiral ligands in enantioselective syntheses.[18,19] 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.[6,20,21] 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.[22]

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.

2. Literature survey

2.1. Pharmacological importance of chiral aminodiols

The importance of aminodiols originates from their significant chemical and pharmacological relevance. Many molecules containing an aminodiol moiety exhibit significant biological activity: for example, chloramphenicol was one of the earliest used antibiotics. Some compounds bearing an aminodiol moiety have proved to be potential HIV protease inhibitors,[23] while others exert renin-inhibitory activity.[24] The natural carbocyclic nucleoside aristeromycin[12] is known for

its antibiotic and antitumor activities, while 1,2-deoxy azasugars from the fagomine[25] family and aminocarbosugars such as valiolamine and their analogs[26] represent an important class of glycosidase inhibitors (Figure 2).

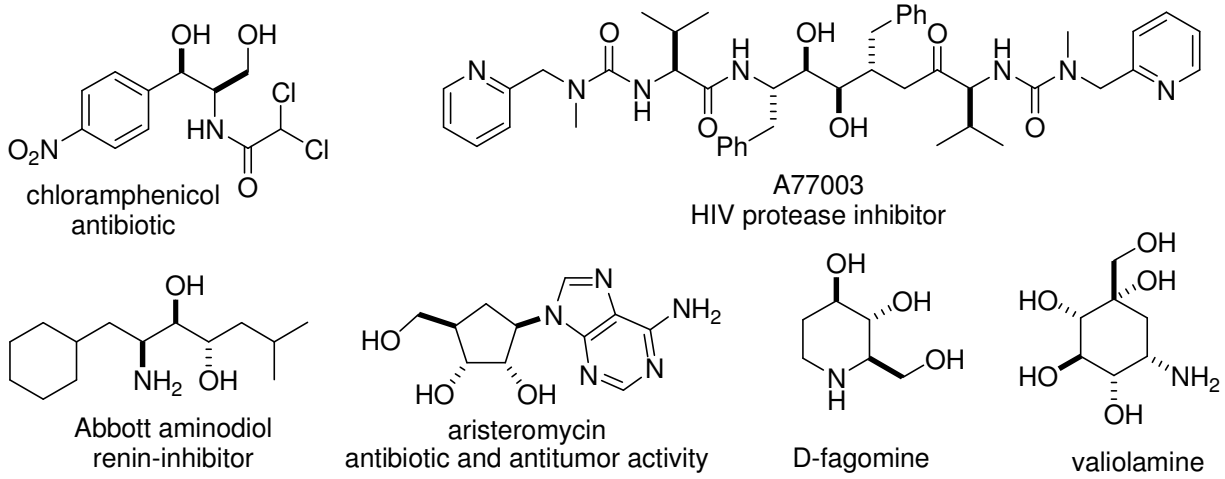
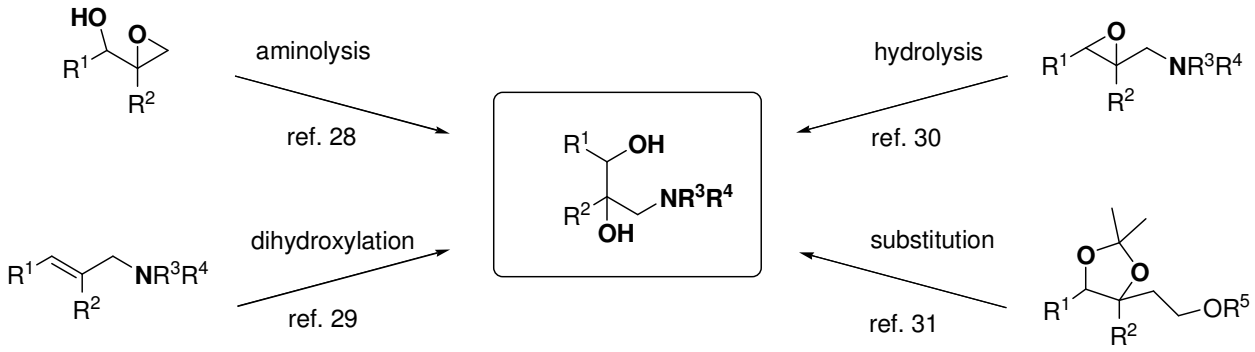


Figure 2

Besides their pharmacological importance, aminodiols can serve as starting materials in the synthesis of biologically active compounds. For the synthesis of Taxotere®, a chemotherapeutic drug, preparation of the side-chain in enantiomerically pure form is required. Pasto *et al.* developed a stereodivergent approach to diastereo- and enamtiomerically pure α-hydroxy-β-amino acids from anti *N*-Boc-3-amino-1,2-diols.[27]

2.2. Synthesis and application of chiral aminodiols

Aminodiols can readily be prepared by several methods, some of the more frequently applied of them being shown in Scheme 1. The aminolysis of epoxy alcohols,[28] the dihydroxylation of amino alkenes,[29] the hydrolysis of epoxy amines[30] and the nucleophilic substitution of a good leaving group[31] are just a few that may be mentioned.



Scheme 1

For the asymmetric synthesis of aminodiols, the most frequently applied method is the asymmetric Sharpless epoxidation of allylic alcohols,[32-35] followed by the regioselective ring opening of epoxy alcohols by various nitrogen nucleophiles (ammonia, amines or azides), resulting in chiral aminodiols.[28,36-41] A moderate number of enantiomerically pure aminodiols and their derivatives are applied as chiral auxiliaries or catalysts in enantioselective transformations (Figure 3).

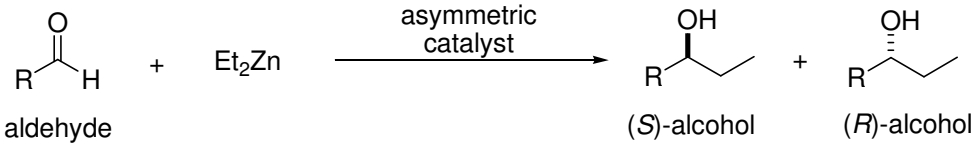
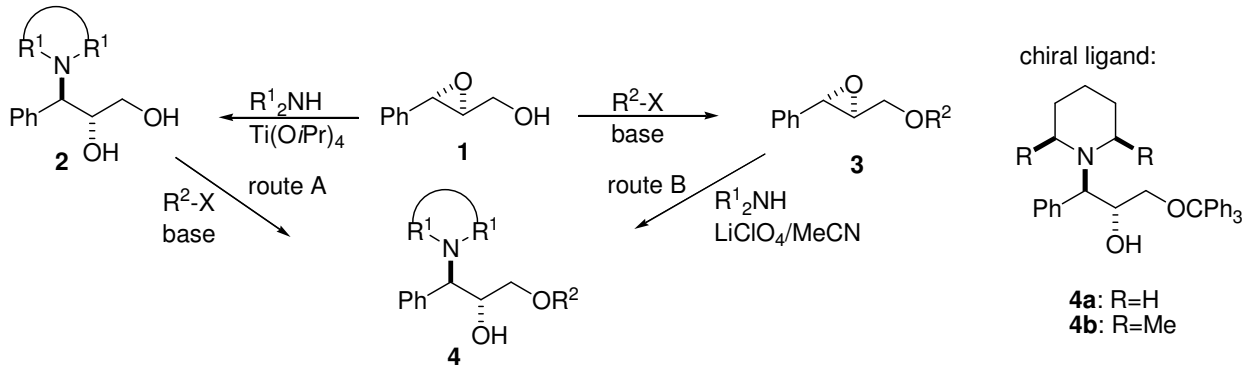


Figure 3

2.2.1. Synthesis of chiral aminodiols

Vidal-Ferran *et al*. reported the synthesis of a library of enantiomerically pure (1*R*,2*R*)-1-dialkylamino-1-phenyl-3-alkoxy-2-propanols **4**, starting from the non-natural chiral compound **1**.[42,43] Compounds **4** contain the structural characteristics of 1,2-amino alcohols and have an extra hydroxy group, a possible additional binding site. Through two alternative synthetic routes, 3-amino 1,2-diols **4** were prepared from the 2*S*,3*S* enantiomer of epoxycinnamyl alcohol **1** obtained by Sharpless epoxidation from cinnamyl alcohol (with full control of the structural and stereochemical parameters; Scheme 2). Derivatives of **4** have been tested (6 mol% ligand) in the enantioselective addition of Et_2Zn to aldehydes in order to identify the structural parameters key to high catalytic activity (Figure 3). Molecular modeling studies have additionally been carried out to improve the ligand design.

Compound **4a** and its modified derivative **4b** were found to be adequate catalysts in the enantioselective addition of Et_2Zn to benzaldehyde. High selectivity was also observed in the formation of (*S*)-1-phenyl-1-propanol (91% *ee* with **4a** and 95% *ee* with **4b**).

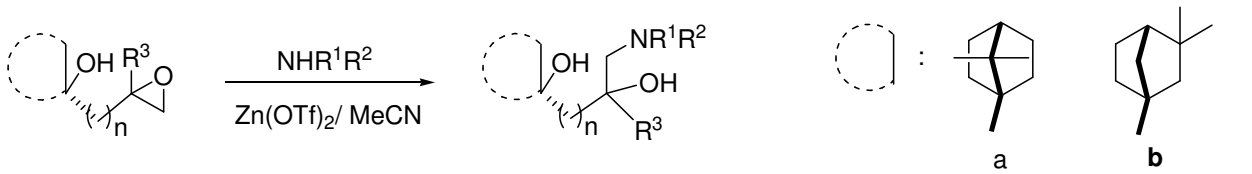


R^1R^1 = -$(CH_2)_4$-; 1'-(*R*)-CH_2OMe-$(CH_2)_4$- ; 1'-(*S*)-CH_2OMe-$(CH_2)_4$-; -$(CH_2)_5$-; -$(CH_2)_6$-; -$(CH_2)_2O(CH_2)_2$-; *i*Pr_2; Bu_2
R^2 = H; Me; CH_2Ph; $CHPh_2$; CPh_3; $SiMe_2Bu^t$

Scheme 2

Following the breakthrough in asymmetric synthesis achieved by Noyori *et al*., who used monoterpene-based chiral ligands in the enantioselective alkylation of benzaldehyde, several chiral ligands derived from readily available optically active monoterpenes were applied in enantioselective transformations.[44] Suitable functional groups and the double bond in the monoterpene structure provide access to further synthetic transformations. Many research groups have studied the functionalization of various monoterpenes. Starting from (+)- and (-)-α-pinene,[4,45] (+)-3-carene,[46] (-)-menthone,[47] (+)-camphor, (-)-fenchone[5] or (+)-pulegone,[6] various β-amino acid derivatives (amino alcohols, amino esters, diamines and aminodiols) have been prepared. [3-6, 20,21,48-53]

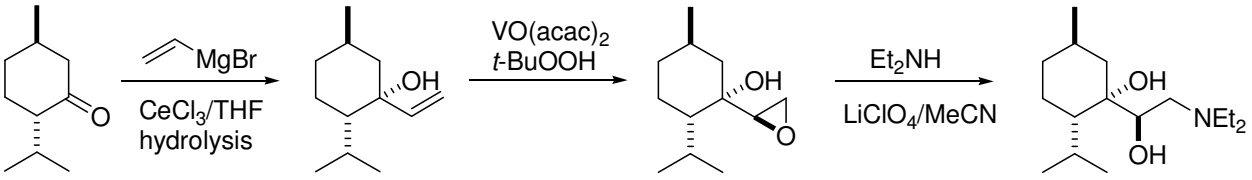
Philipova and co-workers built up the aminodiol structure by using the nucleophilic ring opening of epoxy alcohols derived from (+)-camphor and (-)-fenchone.[54] The aminolysis of epoxy alcohols **5** proceeded with excellent regioselectivity, and retention of the configuration, resulting in various aminodiols **6** (Scheme 3). The catalytic activities of aminodiols were tested (3 mol% ligand) in the addition of Et_2Zn to benzaldehyde (Figure 3). The best *ee* value (*ee* = 80%) was achieved by using the camphor derivative chiral ligand **6a** (n = 0; R^1 = R^2 = Et; R^3 = H), the major product obtained was (*S*)-1-phenyl-1-propanol.



5 a,b **6 a,b** n = 0, 1; $R^1 = R^2 = Et$; $R^3 = H$; Me: (*R*) or (*S*)

Scheme 3

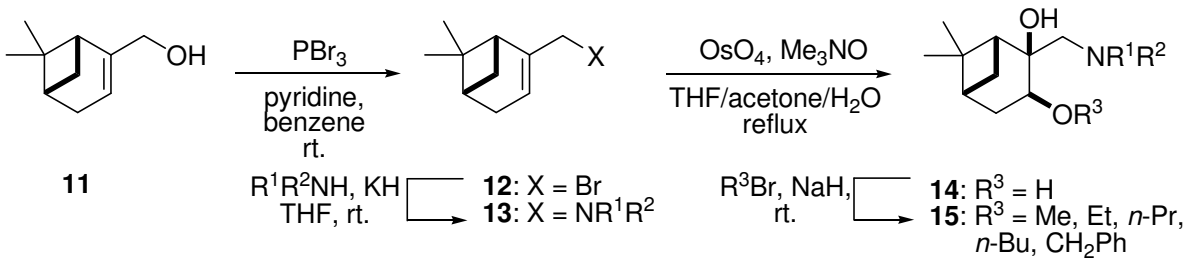
Optically active monoterpene-based aminoalcohols and aminodiols were synthetized from (-)-menthone by Dimitrov *et al*.[47] The preparation of aminodiol **10** as an example is illustrated in Scheme 4. Allylic alcohol **8** was obtained quantitatively as a single diastereoisomer by the addition of the vinyl Grignard reagent to **7**. The epoxidation of the double bond was performed with *t*-BuOOH and $VO(acac)_2$ as catalyst, resulting in **9** with good diastereoselectivity (*de* = 98%). Epoxide ring opening by secondary amines, *e.g.* Et_2NH in the presence of $LiClO_4$, took place with excellent regioselectivity and retention of the configuration (Scheme 4). When aminodiol **10** (3 mol% as ligand) was applied in the addition of Et_2Zn to benzaldehyde, moderate *ee* was observed (*ee* = 40%), whereas the formation of *S*-enantiomer predominated.



7 **8** **9** **10**

Scheme 4

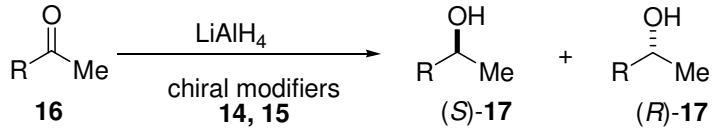
Lu and co-workers found that pinane-type tridentate chiral ligands were excellent catalysts in enantioselective reactions.[55,56] Enantiomerically pure chiral secondary alcohols were obtained by the asymmetric reduction of prochiral ketones or by the addition of Et_2Zn to aldehydes, catalyzed by pinane-based aminodiols derived from (1*R*)-(-)-myrtenol **11**. The reaction of **11** with PBr_3, followed by substitution of the bromo function of **12** with a series of primary or secondary amines, afforded amines **13**, which were converted to aniline-type aminodiols (**14** and **15**) by stereoselective dihydroxylation of the double bond with the OsO_4-Me_3NO system as oxidizing agent (Scheme 5).



R^1= Ph, 2-MeC_6H_4, 2-PrC_6H_4, 2-*t*-BuC_6H_4, 2-$MeOC_6H_4$; R^2 = H, Me, Et, *n*-Bu, Ph;

Scheme 5

Aminodiols **14** and **15** were applied as chiral modifiers in the asymmetric reduction of various ketones (Scheme 6) and as chiral catalysts in the asymmetric alkylation of aldehydes by Et_2Zn (2 mol% as ligand). The results revealed the importance of the amino function and the rigid structure of the pinane skeleton in the asymmetric induction of chiral catalysts. The reduction of ketones was best promoted by ligands **14**, yielding (*R*)-**17** (Scheme 6), while derivatives **15** bearing an alkoxy substituent at C-3 proved to be the best catalysts in the addition of Et_2Zn to aldehydes, giving (*S*)-1-phenyl-1-propanol (Figure 3, R = Ph).



R = Ph, 2-MeC_6H_4, 2-BrC_6H_4, 2-ClC_6H_4, 2-$MeOC_6H_4$, 2-$NO_2C_6H_4$, 2,4-$MeOC_6H_3$, 2,5-$MeOC_6H_3$, 1-naphthyl, 2-furyl, 2-thienyl, PhCH=CH, 1-cyclohexenyl

Scheme 6

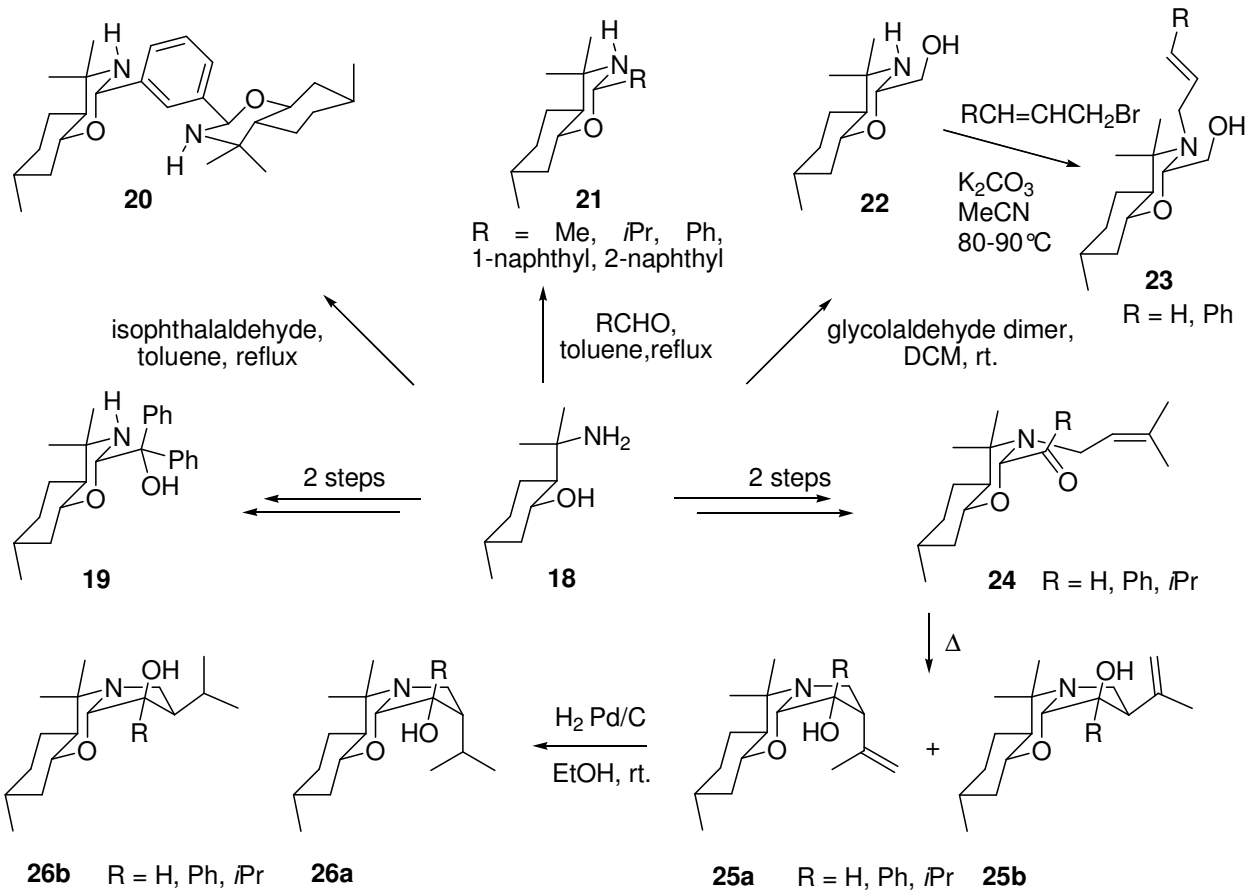
In addition to their synthetic importance, alicyclic aminodiols are valuable starting materials in the synthesis of cycloalkane-fused five- or six-membered heterocycles. Oxazolidines are widely used chiral catalysts in enantioselective synthesis.[57,58] 1,3-Oxazines, which could also be obtained depending on the regioselectivity of the ring-closure process, are promising ligands in the asymmetric alkylation of aldehydes by organozinc, but there have been only a few reports of the application of these heterocycles. [20,59-61] As concerns previous literature data, [20,61] Andres and co-workers prepared chiral perhydro-1,3-benzoxazine derivatives from (-)-8-aminomenthol, in order to examine the catalytic effect of these six-membered heterocycles.[62] Structural diversity was obtained through relatively simple reaction steps (Scheme 7). The condensation of **18** with the appropriate aldehydes took place with excellent diastereoselectivity, giving ligands **19**-**22** and **24**. Compound **22** was alkylated with allyl or cinnamyl bromide to increase the catalytic activity by

N-alkyl substitution. *N*-Prenyl derivative **24** was prepared in two successive steps: the condensation of **18** with phenylglyoxal, followed by *N*-alkylation of the resulting intermediate oxazine with prenyl bromide.

Further transformations led to derivatives with more rigid structures: the thermally induced intramolecular carbonyl-ene cyclization reaction of **24** resulted in a mixture of diastereomers **25a** and **25b**. On variation of the reaction conditions, both enantiomers could be prepared stereoselectively. In order to increase the steric hindrance, the prenyl group in **25** was hydrogenated in the presence of Pd/C, resulting in **26**.[62]

Examination of the catalytic potency and the optimization of chiral ligands **19**-**26** (10 mol% ligand) was performed in the reaction of Et_2Zn and 2-naphthaldehyde (Figure 3). Improvement of the enantioselectivity was observed when ligand **26b** was used. The perhydrobenzoxazine-fused pyrrolidine **26b** (R = Ph) greatly promoted the ethylation of 2-naphthaldehyde (*ee* = 97%), probably because of its distinct rigid structure. Predominantly the *R*-enantiomer of the secondary alcohol was formed. Chiral ligand **26b** also proved to be an efficient catalyst in the addition of Et_2Zn to various aldehydes.[62]

A similar efficient catalytic effect was observed, when chiral ligand **26b** was applied in the enantioselective addition of Me_2Zn to aldehydes.[63] Chiral perhydro-1,3-benzoxazine ligand **25b** (R = *i*Pr) proved an efficient catalyst in the asymmetric methylation of α-ketoesters, providing 96% *ee*.[64] The studies by Andres *et al*. revealed the importance of the oxazine ring in the structure of the ligands for improved enantioselectivity.

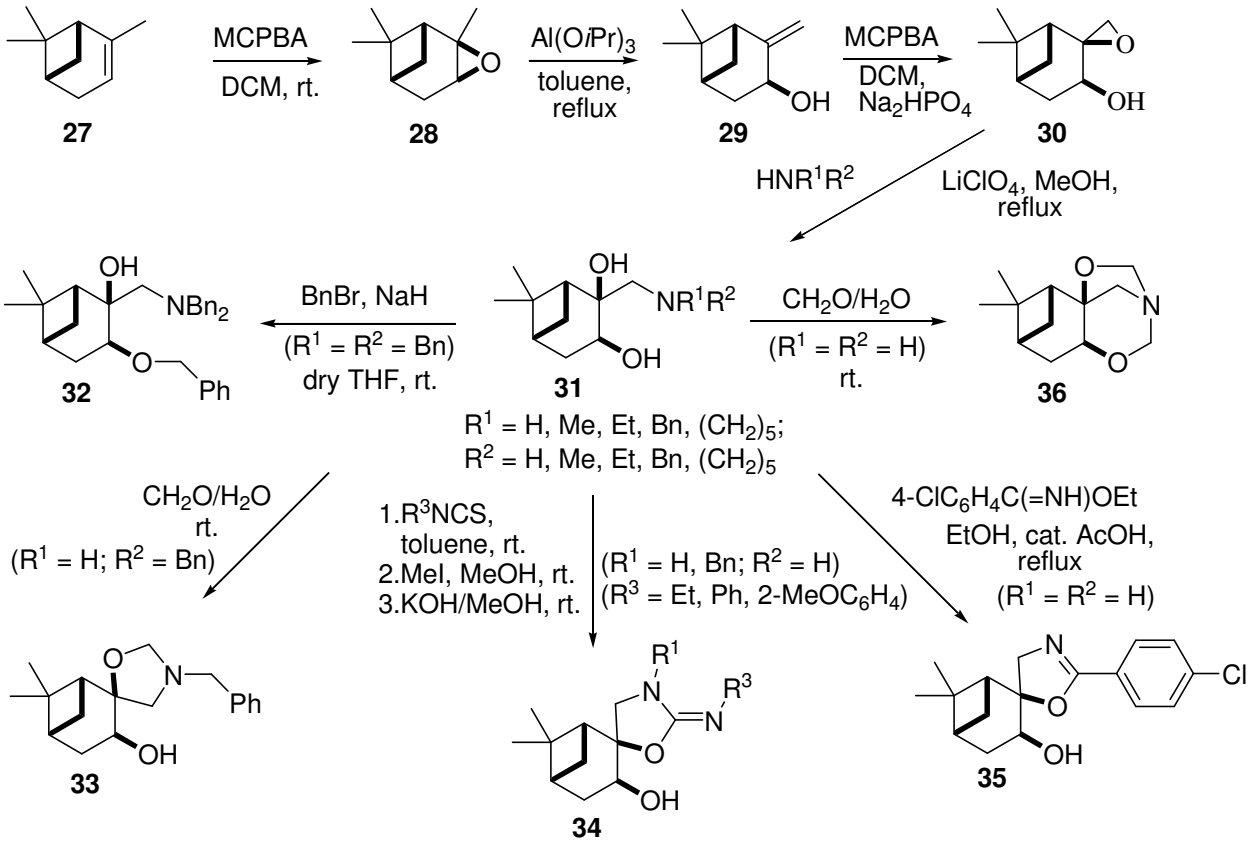


Scheme 7

Further pinane-based derivatives were prepared (Scheme 8) in order to examine their catalytic activity in the asymmetric alkylation reaction mentioned above.[9,45] Starting from (-)-α-pinene **27**, aminodiols **31** were synthetized stereoselectively. The transformation of **27** to key intermediate epoxy alcohol **30** was accomplished via stereospecific epoxidation and rearrangement reactions followed by stereospecific oxirane ring formation.

The aminolysis of **30** led to pinane-based aminodiols **31** when various secondary amines were applied in the presence of $LiClO_4$ as catalyst for the ring-opening process. The structural diversity of aminodiols **31** offered an opportunity to examine the influence of *N*-substituents on the enantioselectivity in the reaction of Et_2Zn to benzaldehyde. Increasing enantioselectivity was observed in the sequence NH_2 < NHR < NRR. *O*-Benzyl derivative **32** was synthetized by regioselective alkylation with benzyl bromide. The regioselectivity of the ring closure of pinane-type aminodiols **31** was also studied, since they are useful starting materials in the formation of five- or six-membered heteocyclic systems. Through the treatment of **31** (R^1 = H, R^2 = CH_2Ph)

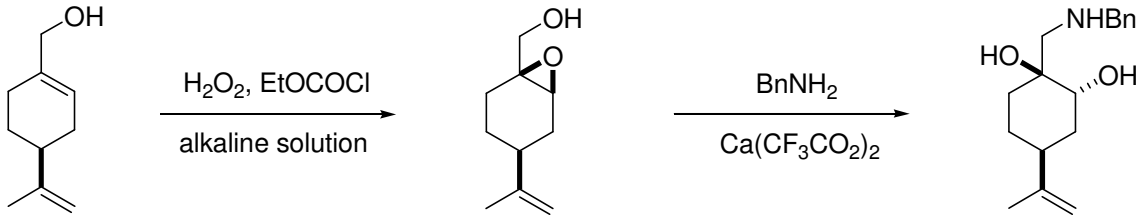
with formaldehyde, the quaternary hydroxy group was incorporated, providing spiro-fused oxazolidine **33** with excellent regioselectivity (the formation of 1,3-oxazine was not detected). The asymmetric induction was comparably lower when either of the hydroxy groups was *O*-alkylated (**32** and **33**). These results revealed the importance of the tridentate aminodiol structure in the catalytic activity of monoterpene-based ligands, in comparison with those containing a 1,3-amino alcohol moiety. In order to study the tendencies of aminodiols **31** to furnish either spiro-oxazolidines or 1,3-oxazines, derivatives **33**-**36** were prepared. Aminodiols **31** underwent ring closure (in the three-step reaction) with isothiocyanates, imidates or aldehydes. In each case formation of the spiro-oxazolidine derivative was preferred. In the case of **31** (when $R^1 = R^2 =$ H), the ring closure of the primary amino and hydroxy groups resulted in tetracyclic compound **36**.



Scheme 8

A further synthesis of an aminodiol based on a natural monoterpene derivative is presented in Scheme 9. The transformation of (*S*)-perillyl alcohol **37** to aminodiol **39** was reported by Outouch *et al*. and the crystal structure was described. Epoxidation of the double bond, followed

by aminolysis of the oxirane ring by benzylamine in the presence of $Ca(CF_3CO_2)_2$ as catalyst led to the chiral aminodiol. An unexpected rearrangement was observed: the major product isolated was the 3-amino-1,2-diol derivative **39**.[65]



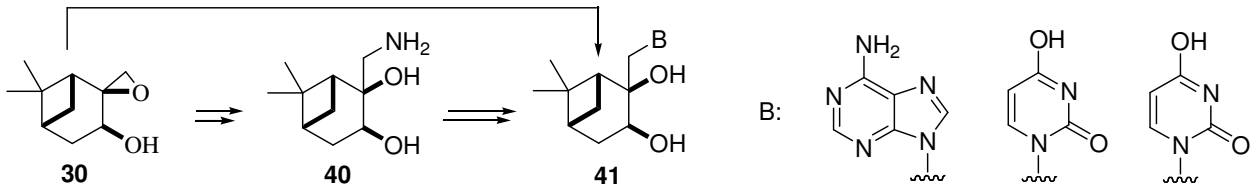
37 **38** **39**

Scheme 9

2.2.2 Application of chiral aminodiols

Pedrosa *et al*. prepared enantiopure *N*-containing heterocycles through the use of 1,3-oxazines derived from (-)-8 aminomenthol **18** as chiral auxiliaries.[6,66,67]

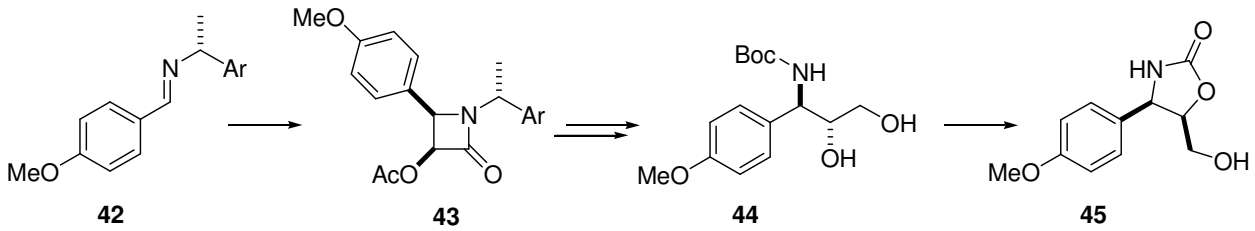
Both enantiomers of sterically constrained bicyclic pinane-based aminodiols **40** were used as building blocks in the synthesis of carbocyclic nucleoside analogs **41**.[68] Scheme 10 presents the stereoselective synthesis of one of the enantiomers.



30 **40** **41**

Scheme 10

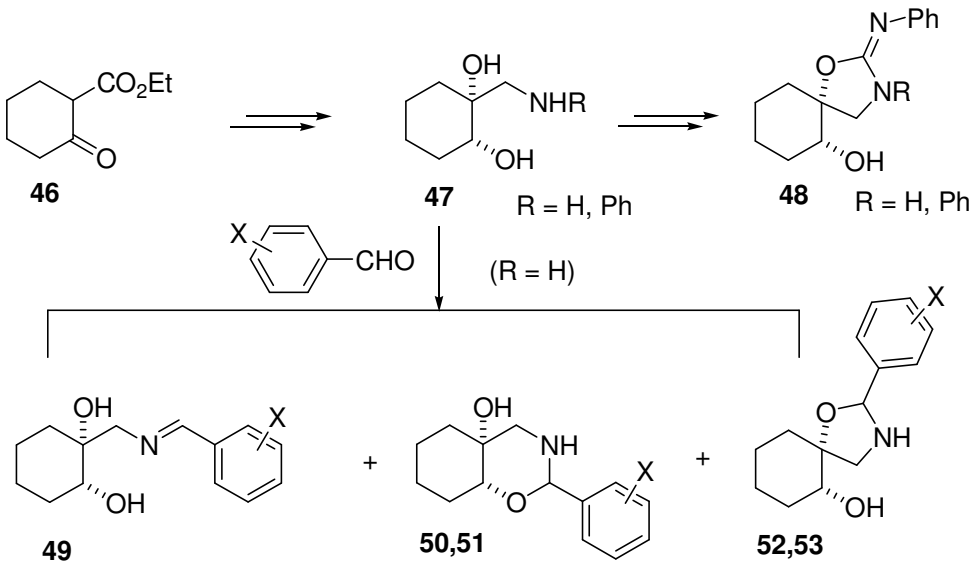
Naturally-occurring oxazolidinones, (-)-cytoxazone **45** and its analogs, were prepared by Grajewska *et al*. via various synthetic routes.[13] (-)-Cytoxazone is a potent cytokine modulator of the secretion of T_H2 cytokine, a microbial metabolite isolated from cultures of *Streptomyces* species. In recent years, synthetic strategies for the preparation of cytoxazone have been reviewed.[13] Scheme 11 presents an example of a synthetic pathway for **45**. Starting from (*R*)-anisaldimine **42**, chiral β-lactam **43** was prepared by the cycloaddition of O-acetoxyacetyl chloride, and then transformed in five synthetic steps, including the methanolysis of β-lactam, *N*-debenzylation, *N*-Boc group introduction, reduction and the Mitsunobu reaction, to afford aminodiol **44**. The desired (-)-cytoxazone **45** was achieved by the cyclization of **44**.



Scheme 11

Aminodiols can participate in the formation of heterocycles. Aminodiols with functionalities at positions 1, 2 and 3 can yield oxazolidines or 1,3-oxazines, depending upon which hydroxy group participates in the ring-closure procedure. As shown in Scheme 8, the ring closure of pinane-based aminodiols **31** furnished only the spiro-oxazolidines **33**-**36**. The preparation of (-)-cytozazone **45** mentioned above (Scheme 11) is another example of the synthesis of heterocycles from aminodiols.

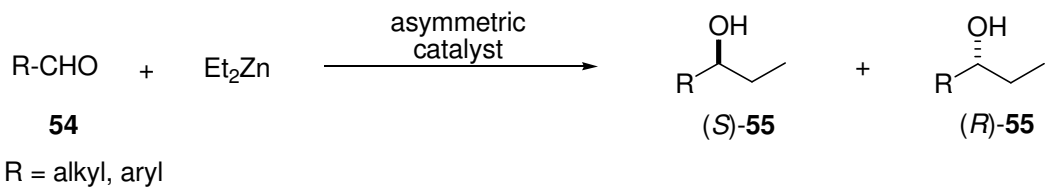
The tendencies of *cis*- and *trans*-1-aminomethylcyclohexane-1,2-diol to form either oxazolidines or 1,3-oxazines were examined by the reaction of **47** with phenyl isothiocyanate. The spiro derivatives **48** were obtained regioselectively, and formation of the 1,3-oxazine was not detected. When various aromatic aldehydes were applied the ring closure of **47** provided a mixture of five components: Schiff base **49**, the two epimers of 1,3-oxazine (**50** and **51**) and the spiro-oxazolidine epimers (**52** and **53**). The ring-chain tautomeric system was characterized by ^{1}H-NMR measurements. Scheme 12 depicts only the transformation of the *cis* isomers; the *trans* isomers were prepared in an analogous way.[22]



Scheme 12

2.2.3. C-C bond-forming model reaction for testing the catalytic activity of new asymmetric catalysts

The increased demand for enantiopure compounds has resulted in a significant development in the field of asymmetric synthesis, which includes three main approaches: chiral pool synthesis, the chiral auxiliary method or asymmetric catalysis. However, in the last two decades asymmetric catalysis has become the most investigated topic in organic chemistry. Among the asymmetric catalytic reactions, the catalyzed enantioselective addition of dialkylzinc to prochiral carbonyl groups has gained great importance, since it produces valuable optically active secondary alcohols,[18] which can be used as chiral building blocks in the preparation of biologically active compounds. In addition, the enantioselective alkylation of aldehydes (Scheme 13) has become a classical model reaction, providing a convenient method for testing new chiral catalysts.



Scheme 13

Following the pioneering work of Oguni and Omi[69] a great number of chiral catalysts have been investigated.[3-5,18,21,47,49,50,53,61] Since Noyori *et al*. established the mechanism of catalytic Me_2Zn addition to benzaldehyde in the presence of DAIB,[44] it is well known that 1,2-amino alcohols form an *in situ* generated five-membered zinc complex. According to the theoretical studies of the reaction mechanism and the possible transition state models, the amino alcohol moiety acts as a Lewis base which forms Lewis acidic zinc chelates. These zinc chelates activate both the carbonyl substrates and the organozinc reagents and also control the stereochemistry.[70] With 1,3-ligands as catalysts, in which case a more flexible six-membered zinc chelate is formed, the transition state model of such ligands is less well explored. Chiral aminodiols, which combine the chemical properties of 1,2- and 1,3-amino alcohols, have also proven to be efficient chiral catalysts, although their application too has been studied relatively sparsely. There are only a few examples of the use of aminodiols and derivatives as asymmetric catalysts in enantioselective transformations. Transition state models proposed for the chiral ligands mentioned above (**4**, **14**, **26b** and **31**) and applied in the enantioselective addition of Et_2Zn to aldehydes are presented in Figure 4. [8,22,43, 54-56, 63,64]

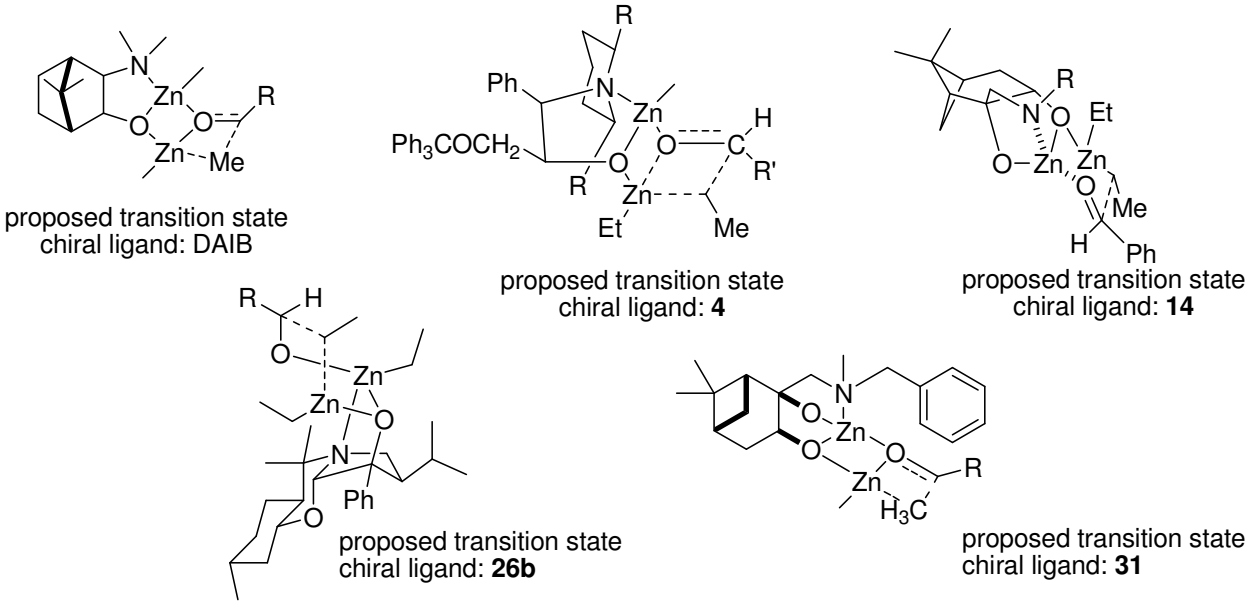


Figure 4

Aminodiols and their derivatives have found diverse application as catalysts in C-C bond-forming reactions.[18,71] As an example, Braga *et al*. used a chiral oxazoline ligand in the ethylation of aromatic and aliphatic aldehydes.[60] Pericas and co-workers used a chiral aminodiol derivative

Schiff base ligand in the enantioselective reactions of Me_3SiCN with aldehydes.[72] In the addition of dialkylzinc to imines, they reported the effectiveness of ligand **4a**,[73] and they additionally applied the polymer-supported **4b** as catalyst in Et_2Zn addition to aliphatic and aromatic aldehydes. The resulting *ee* values were slightly lower than those obtained by using the corresponding **4b** in a homogeneous phase. Among the advantages of polymer-supported catalysts is the easy recovery and simplified product purification.[74,75]

2.3. Pharmacological importance and application of bicyclic β-amino acid derivatives

Several β-amino acid derivatives such as β-amino amides are rarely tested as catalysts or chiral ligands in enantioselective transformations.[76-79] However, the pharmacological importance of β-amino acids and their derivatives is noteworthy. Monoterpene-based β-amino acids and esters exhibit marked anticonvulsant activity,[80] while the apopinene-based urea and thiourea derivatives possess MDR inhibitor activity,[81] the monoterpene-based β-amino amide has been reported to be a tyrosine kinase Axl inhibitor,[82] and the β-amino amides synthetized by Curtin *et al*. are known as KDR and Aurora B kinase inhibitors (Figure 5).[83]

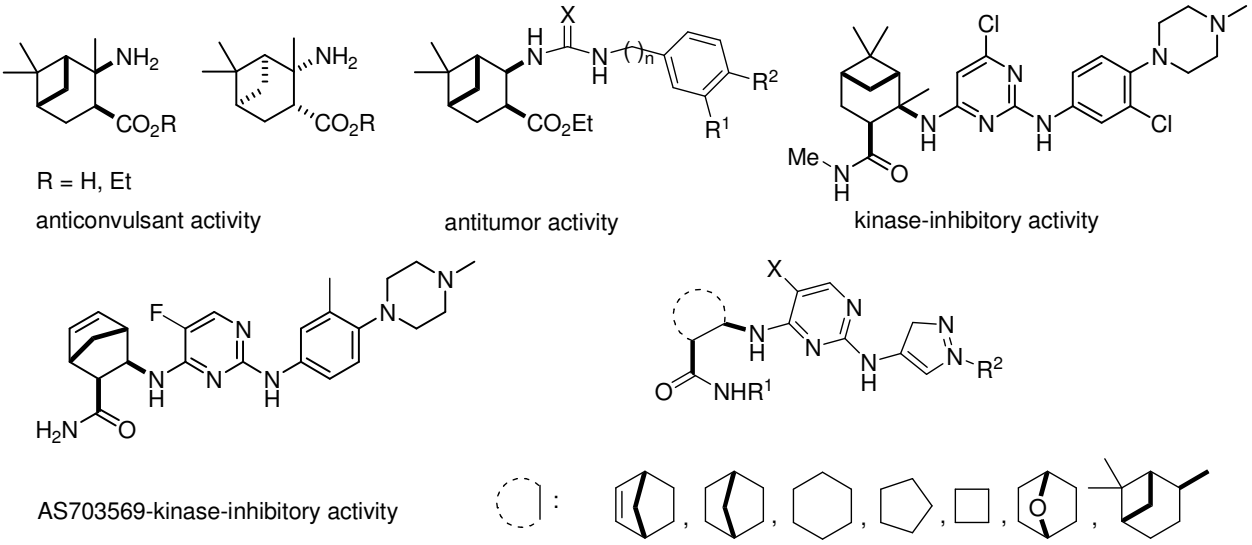
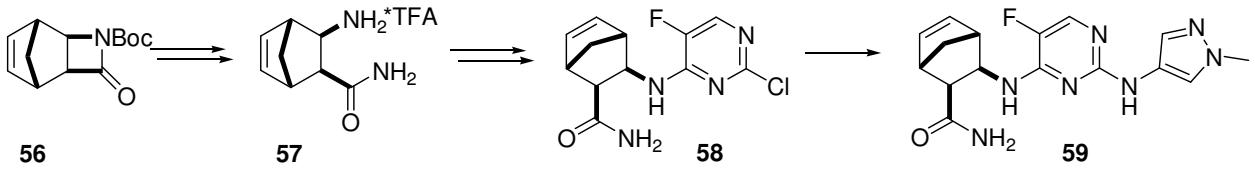


Figure 5

One example of the synthesis of racemic pyrazole diaminopirimidines reported by Curtin *et al*. is illustrated in Scheme 14.[83] Racemic β-lactams are used as starting materials. In subsequent synthetic steps, β-amino amide **57** was prepared by the ring opening of Boc-protected β-lactam and transformed to target compound **59** through successive substitutions.



Scheme 14

The kinase inhibitor activity of pyrazolo pyrimidine **59** has been tested; it showed potent activity against KDR and Aurora B kinase.

2.4. Synthesis and application of chiral β-amino acid derivatives and 1,3-diamines

Since the discovery of the pharmaceutical importance of cyclic β-amino acids, more attention has been paid to the asymmetric synthesis and transformations of such building blocks.[7,84] The incorporation of chirality into β-amino acids could be achieved from natural sources such as enantiomerically pure monoterpenes.[7], Further chemical modifications are therefore allowed while the chirality of the monoterpene skeleton is intact. Reported studies have revealed that optically active β-amino acids could be adequate starting materials for the synthesis of 1,3-bifunctional ligands serving as chiral ligands in enantioselective transformations.[20,85,86]

While the synthesis and application of alicyclic 1,2-diamines have received great attention and numerous examples have been reported,[77,87-91] the preparation and use of 1,3-diamines is less well explored.[76,92]

Carbocyclic derivatives such as cyclopentane- and cyclohexane-1,2-diamines are widely used as catalysts in asymmetric syntheses. They also tend to display potent antitumor and antiviral activity.[14,15,93-96] Carene-based analogs are diamines that are structurally correlated with 1,2-diaminocyclohexane derivatives. Monoterpene-based 1,2-diamines were prepared by Cimarelli *et al*. by simple synthetic steps, starting from (4*S*)-(-)-limonene-oxide and (+)-3-carene, and proposed for further examinations as catalysts in asymmetric syntheses. [52,97] Asami and co-workers synthetized chiral di- and triamines from (*S*)-proline or from (*S*)-indoline-2-carboxylic acid, and applied them as chiral catalysts in the enantioselective addition of Et_2Zn to aldehydes.[98,99] They reported that ligands containing an aromatic amino group improves the selectivity in comparison with those bearing an aliphatic amino group, due to the higher acidity of the aromatic nitrogen proton.

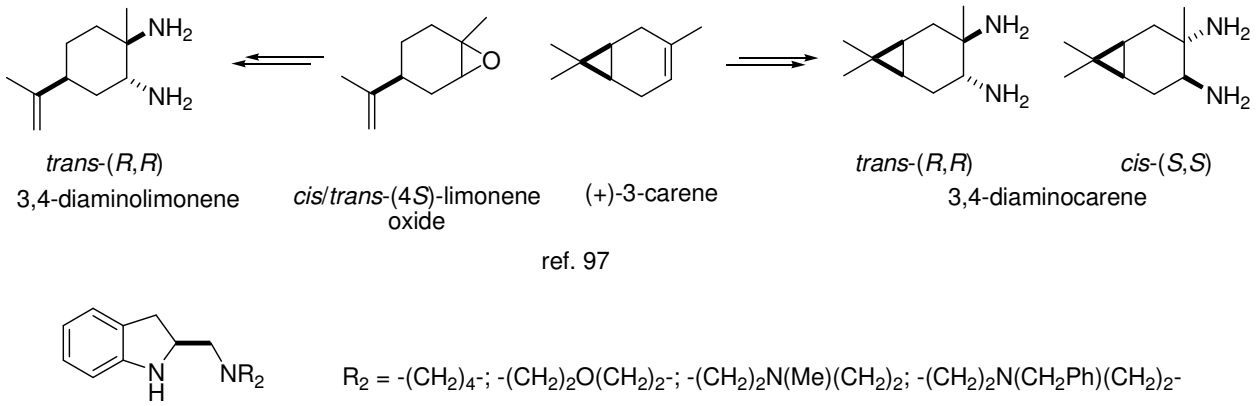
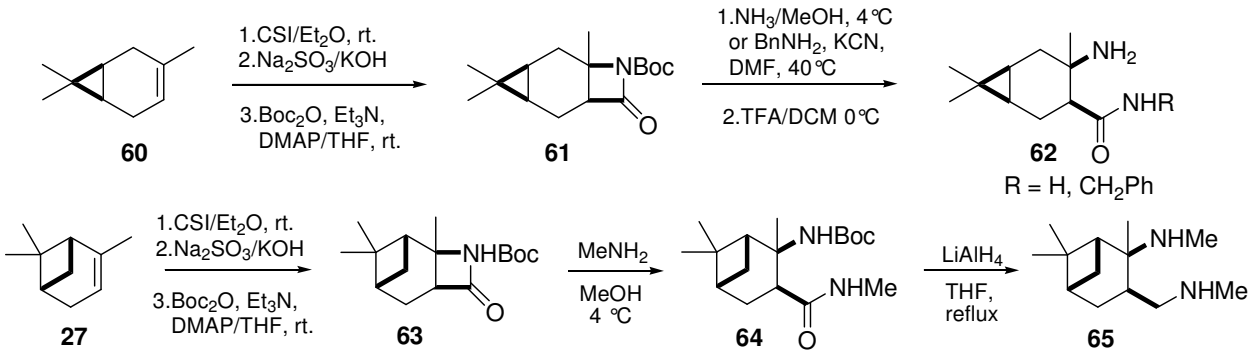


Figure 6

As the proton of the sulfonamide function is more acidic than the aromatic one, it is obvious that the use of *N*,*N*'-disulfonated promoters has been extensively researched.[90,100-103] However, only a few examples are known for the application of chiral monosulfonated diamines.[89,104]

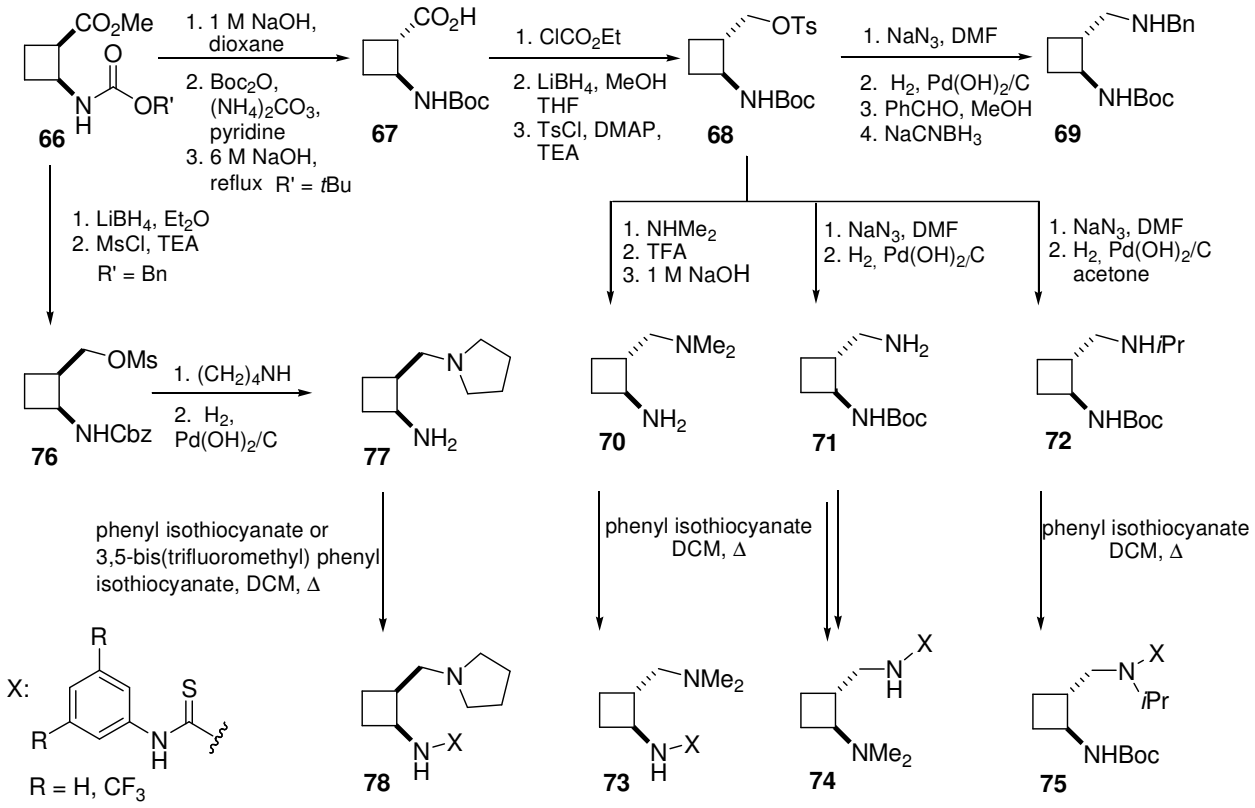
Various methods are available for the synthesis of 1,3-diamines; the most frequently applied approach involves the chemical modification of β-amino acids.[7]

β-Amino acid derivatives were prepared by Fülöp and co-workers using enantiopure, commercially available monoterpenes as chiral sources (Schemes 8 and 15). The facile approach to chiral β-lactams involves the 1,2-dipolar cycloaddition of chlorosulfonyl isocyanate (CSI) to the double bond of a starting monoterpene such as (+)-3-carene or (+)- and (-)-α-pinene. Enantiopure monoterpene-fused β-lactams **61** and **63** were synthetized, profiting from the fact that the addition proceeds regio- and stereoselectively[105] and the chiral information on the monoterpene skeleton is highly transferred. Boc-activated azetidinones **61** and **63** underwent nucleophilic ring-opening procedures, resulting in β-amino amides **62** and **64**. Reduction of β-amino amide **64** provided the pinane-based 1,3-diamine **65**, which was applied as a chiral catalyst in the enantioselective addition of Et_2Zn to aromatic aldehydes. However, no enantioinduction was observed in the case of **65**. The major advantage of the pinane-based derivatives over carane-based compounds is that both enantiomers of α-pinene are commercially available (only the preparation of (-)-α-pinene derivatives are presented in Scheme 15). These β-amino acid derivatives could serve as chiral building blocks in the asymmetric synthesis of potential pharmacons and could also be used as chiral auxiliaries in enantioselective syntheses.[45,46]



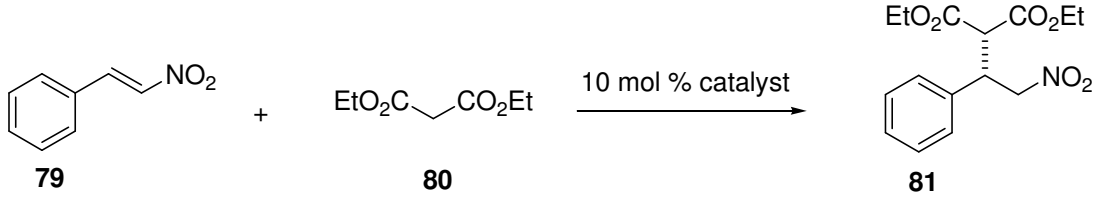
Scheme 15

The simplicity of the modification of the functional groups in β-amino acids makes these compounds promising precursors in the syntheses of 1,3-diamines. The group of Ortuno reported the stereoselective preparation of *cis*- and *trans*-cyclobutane-based 1,3-amino alcohols and 1,3-diamines from protected chiral β-amino acid **66**.[92] The synthetic approach which led to differently substituted *trans*-diamines **69**-**72** involves successive steps, such as isomerization, reduction and substitution; a simpler way was chosen for the preparation of *cis* isomer **77** (Scheme 16).



Scheme 16

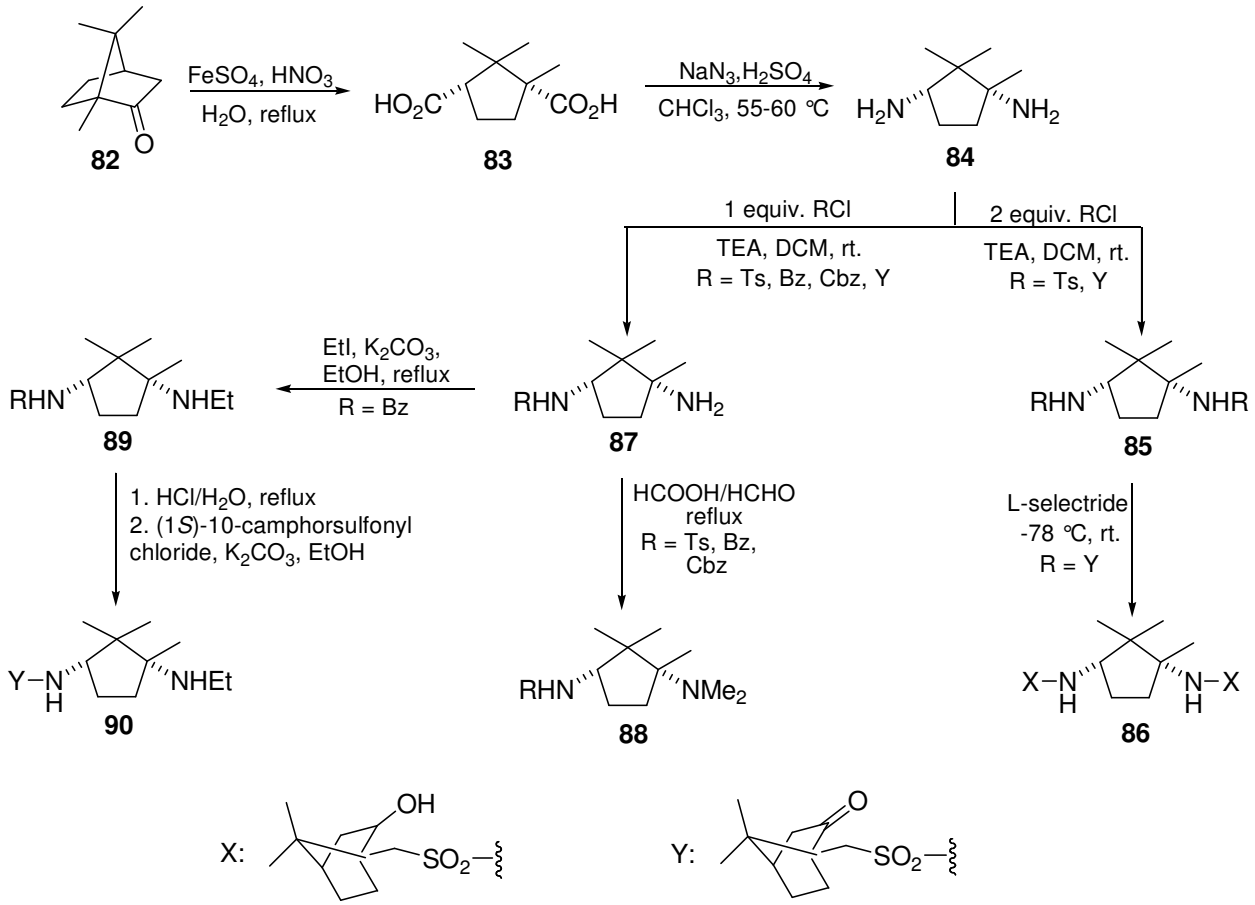
To examine the possible application of these chiral synthons, diamines **69**-**72** and **77** were transformed to thiourea derivatives **73**-**75** and **78** applied as organocatalysts in enantioselective Michael addition (Scheme 17). In comparison with catalysts **73**-**75**, thiourea derivative **78** gave better results, but with moderate asymmetric induction (*ee* = 50%).



Scheme 17

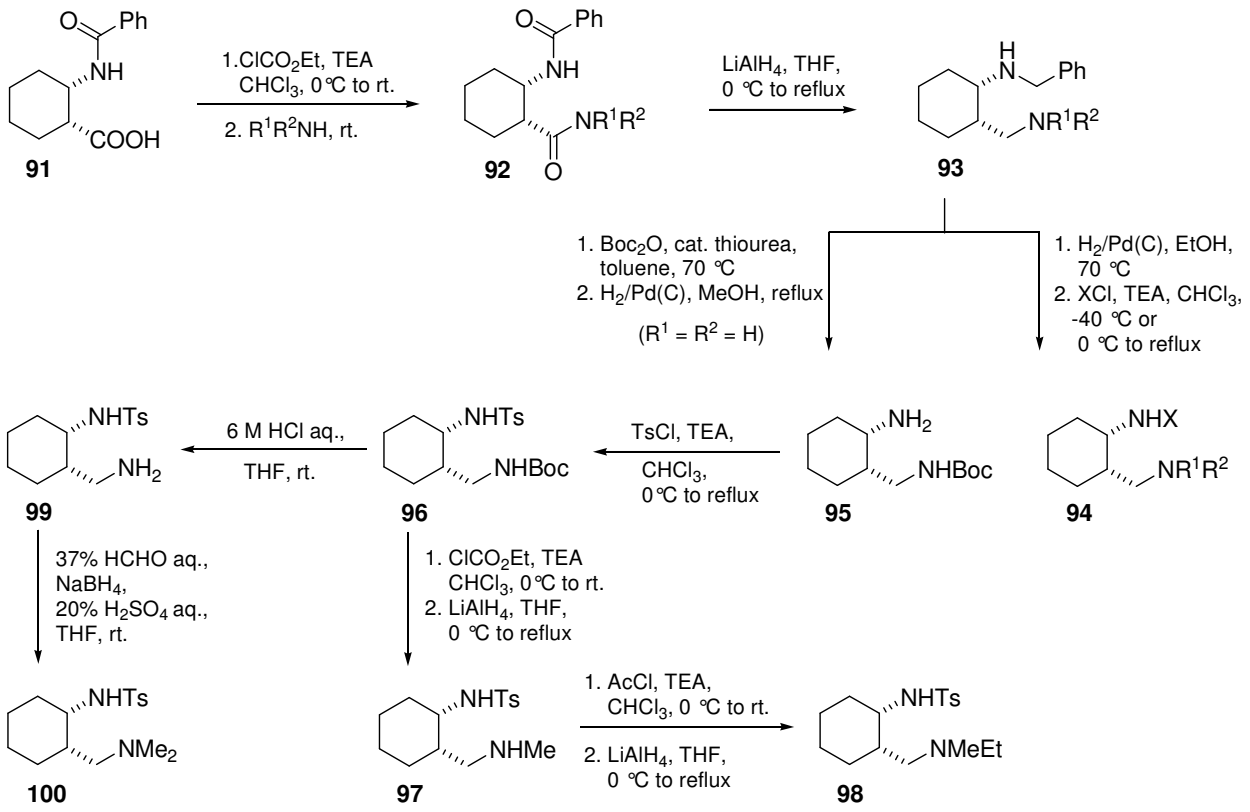
Mono- and disubstituted 1,3-diamines were synthetized by Murtinho *et al*. starting from 1*R*-(+)-camphor **82** (Scheme 18).[76] Diamine **84** was prepared in two sequences via (+)-camphoric acid **83**. The consecutive substitutions led to monosulfonamides, aminoamides and aminocarbamates **87**, by applying 1 equivalent of tosyl, (+)-camphorsulfonyl or benzoyl chloride, respectively. The reaction of **84** with the corresponding sulfonyl chloride provided disulfonamides **85**; further

transformations gave disulfonamide **86**. Bismethylation of **87** (when R = Ts, Bz or Cbz) resulted in compound **88**, while alkylation of **87** (when R = Bz) followed by hydrolysis of the benzoyl group and then substitution led to monosulfonamide **90**. Chiral ligands **85**-**90** were tested in the enantioselective ethylation of benzaldehyde (Scheme 13), producing modest to excellent *ee* values (*ee* = 21-96%). The best result was achieved by applying aminoamide **89** (*ee* = 96%). The presence of a bulky substituent on position 3 of the cyclopentane ring and one ethyl group on amino function at position 1 was determinant for efficient catalytic activation.



Scheme 18

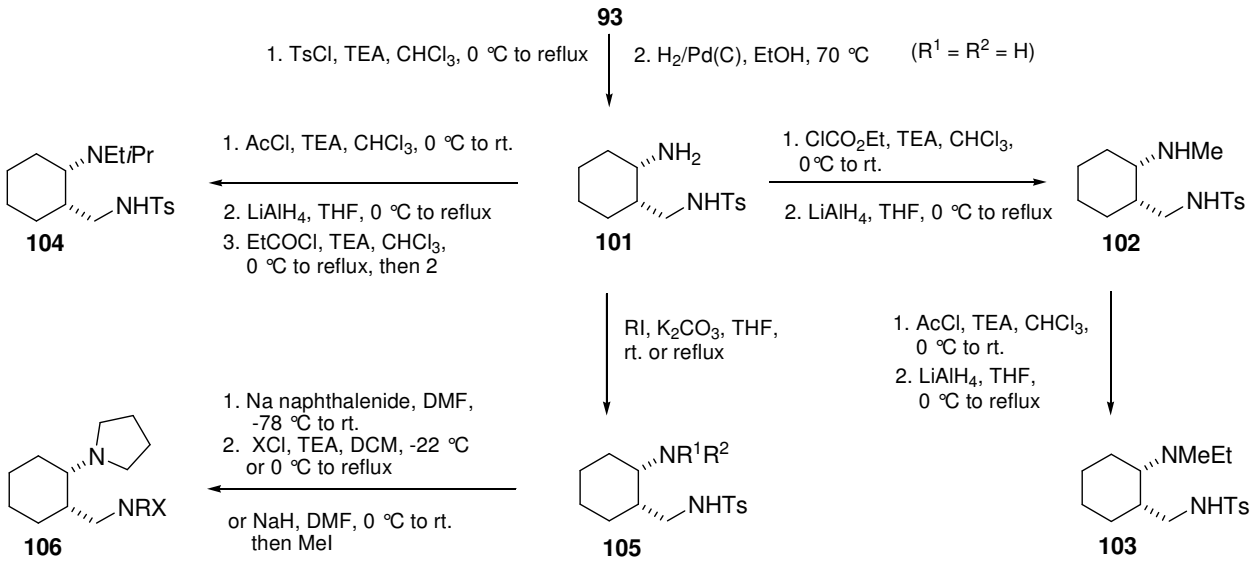
Hirose and co-workers reported the synthesis of regioisomeric 1,3-amino sulfonamides from enantiopure *N*-protected β-amino acid **91**.[106] Amidation followed by reduction led to cyclohexane-based diamines **93** (Scheme 19). The resulting diamine **93** was applied in the synthesis of amino sulfonamides. The reaction pathway of regioisomers containing the sulfonylated cyclohexylamino moiety and the differently substituted cyclohexylmethylamino function is presented in Scheme 19.



92, **93**: $R^1 = R^2$ = H, Me, Et; R^1R^2 = -$(CH_2)_4$-, -$(CH_2)_5$-; **94**: $R^1 = R^2$ = Me; Et; R^1R^2 = -$(CH_2)_4$-, -$(CH_2)_5$-; X: Ts, Ms, Tf

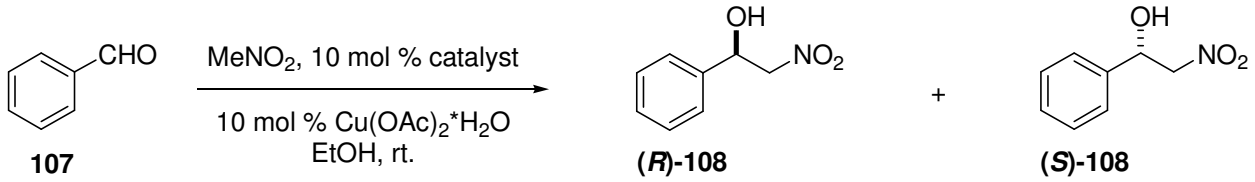
Scheme 19

The positions of the amine and sulfonamide groups are exchanged in regioisomers **101**-**106** (Scheme 20). 1,3-Amino sulfonamides **94**, **97**-**100** and **101**-**106** were tested as chiral ligands in the enantioselective additions of Et_2Zn to aldehydes (Scheme 13). It was shown that switching the position of amino and sulfonamide groups in the ligands with identical absolute configuration afforded secondary alcohols **55** with opposite stereochemistry. The most efficient catalyst **100** gave (*S*)-1-phenyl-1-propanol with 94% *ee*, and the *R* enantiomer of the product was achieved with 98% *ee* by using ligand **106** (R = H, X = Ts). It was found that the presence of tertiary amino and *p*-toluenesulfonyl groups was necessary for optimal catalytic activity.



Scheme 20

The diamines presented above were also successfully applied as ligands in the Cu-catalyzed enantioselective Henry reaction, providing the *R* enantiomer as the major product in 91% *ee* (Scheme 21).[107]

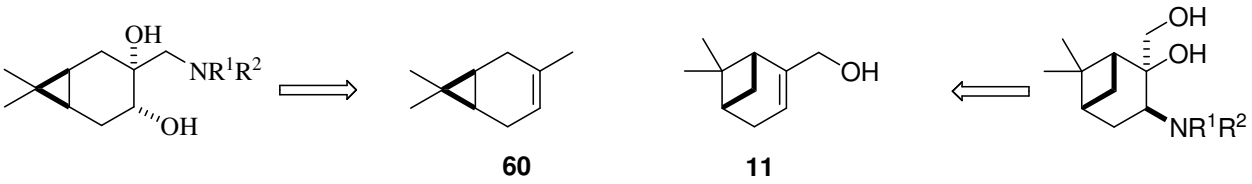


Scheme 21

3. Results and Discussion

3.1. Synthesis of carane- and pinane-based bifunctionalized tridentate ligands

As concerns the synthetic strategy for the preparation of monoterpene based 3-amino-1,2-diols, we preferred the use of enantiopure, commercially available starting materials such as (+)-3-carene **60** and (1*R*)-myrtenol **11**. When stereoselective transformations are applied, the optical purity of the compounds obtained remains identical to the enantiomeric purity of the starting monoterpenes.



60 **11**

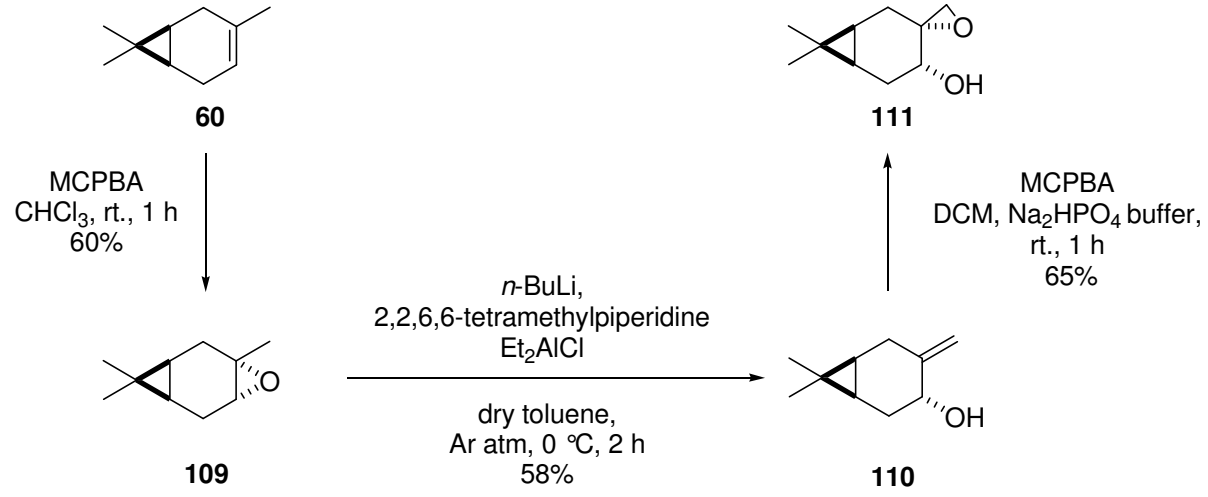
(1*S*)-(+)-3-carene
99% optical purity

(1*R*)-(-)-myrtenol
95% optical purity

Scheme 22

3.1.1. Synthesis of carane-based aminodiols

In the first step of the synthesis of carane-based aminodiols, (+)-3-carene **60** was epoxidized by MCPBA, according to literature methods.[108] The epoxidation proceeded stereospecifically resulting exclusively in endo carene oxide **109** (Scheme 23).



Scheme 23

Epoxides containing a H atom in the α position relative to the epoxide ring could be rearranged into allylic alcohols in the presence of base. The mobility of the allyl H is increases in the sequence $CH < CH_2 < CH_3$.[109]

In view of the above-described mechanism, the expected product in the rearrangement of **109** is the allylic alcohol **110**. Before use of the synthetic protocols described above for the preparation of **110** (Scheme 23), various experiments were performed. In accordance with the combination of literature methods[8,110] applied for other monoterpene epoxides, epoxy carane **109** was subjected to allylic transformation by applying a less expensive procedure: with $Al(O\textit{i}Pr)_3$ in 1 mol% in dry toluene at reflux temperature, described as a successful method for α-pinene oxide. Unfortunately, no reaction was observed. Increasing the amount of $Al(O\textit{i}Pr)_3$ to 5 mol% did not lead to the desired product, and the reaction with Et_2NLi in *t*-BuOH and dry THFwas also unsuccessful.[109]

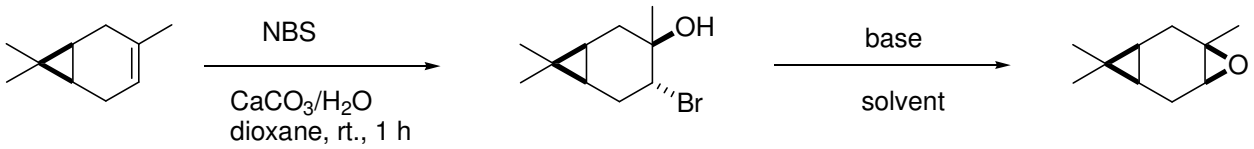
Therefore, the most expensive method had to be applied. Epoxy carene **109** was transformed to the desired allylic alcohol **110** with high efficiency by the action of diethylaluminium tetramethylpiperidine formed *in situ* under the applied reaction conditions. This reagent was formed by the addition of the *n*-BuLi solution in hexane to a solution of 2,2,6,6-tetramethylpiperidine in dry toluene at low temperature, followed by the addition of Et_2AlCl. Compound **109** participated readily in allylic rearrangement, in accordance with the literature data.[111] The transformation was diastereoselective, as **110** was confirmed by 2D NMR spectroscopy

Epoxidation of allylic alcohol **110** took place stereospecifically with MCPBA in DCM (Scheme 23). Only diastereoisomer **111** was formed. The stereochemistry of this new compound was established by NOESY NMR spectroscopy.

The isolated product **111** was purified by vacuum distillation since column chromatography led to decomposition on silica gel or Al_2O_3.

New, optically active epoxy alcohol **111** was regarded as a valuable starting compound in further transformations toward chiral aminodiols.

As an extension of the syntheses we attempted to prepare diastereoisomer **113** by applying literature methods. The synthetic protocol used was hydroxy bromination by NBS, followed by base-mediated intramolecular cyclization.[112]

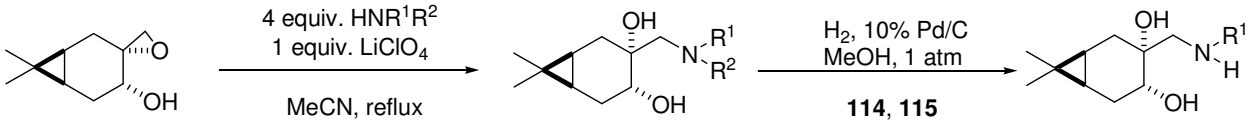


60 **112** **113**

Scheme 24

In the first instance, **60** was converted by 1.2 equivalents of NBS to bromohydrin **112**. The reaction conditions included 1.2 equivalents of $CaCO_3$ suspended in a H_2O/dioxane mixture as solvent. The isolated product was employed in the next step without purification. Unfortunately, we failed to synthetize the epoxy carane **113**. Neither aq. NaOH, nor NaOMe in MeOH proved to be adequate for base-mediated intramolecular S_{N2} cyclization.

Aminolysis of **111** with primary and secondary amines was performed in the presence of $LiClO_4$ as catalyst. The ring-opening procedure was influenced by steric and electronic factors and took place in a highly regioselective manner. The nucleophilic attack of amines occurred at the less hindered and less substituted carbon atom, providing aminodiols **114**-**121** with defined stereochemistry (Scheme 25). To increase the steric hindrance, bulky substituents were introduced on the amino group, and in the cases of aminodiols **117**-**120** an additional chiral center was built in (Table 1: Entry 4-7). However, a low yield was observed in the case of **120** (18%), probably because of the strong steric hindrance of the substituents, while aminolysis of **111** gave aminodiols in acceptable to good yields in most cases (reaction yields varying from 18% to 68%; Table 1). Debenzylation of the corresponding *N*-benzyl-*N*-methyl aminodiol **114** and *N*,*N*-dibenzyl aminodiol **115** was accomplished with 5% Pd/C under 1 atm of H_2 at room temperature, affording **122** and **123** in moderate and good yield, respectively (Table 1: Entries 9 and 10; Scheme 25).



111 **114-121** **114**, **115** **122, 123**

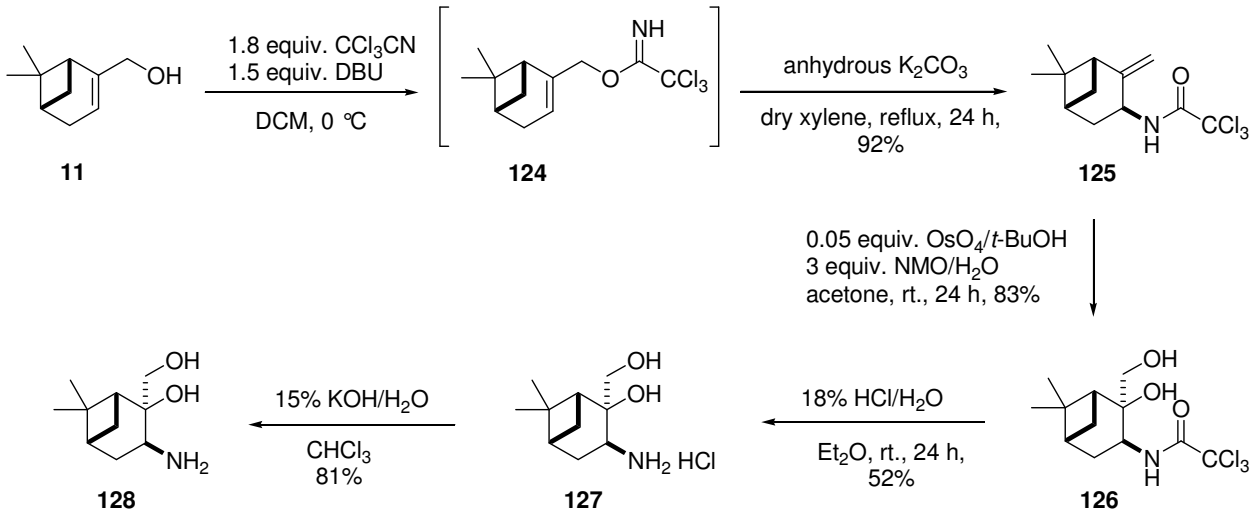
Scheme 25

Table 1. Aminodiols **114**-**123** obtained from **111** by aminolysis or from **114** and **115** by hydrogenolysis

Entry	Compound	R^1	R^2	Yield (%)
1	**114**	Me	CH_2Ph	65
2	**115**	CH_2Ph	CH_2Ph	68
3	**116**	H	CH_2Ph	70
4	**117**	CH_2Ph	CH(Me)Ph (*R*)	38
5	**118**	CH_2Ph	CH(Me)Ph (*S*)	29
6	**119**	H	CH(Me)Ph (*R*)	47
7	**120**	H	CH(Me)Ph (*S*)	18
8	**121**	H	*i*Pr	31
9	**122**	Me		37
10	**123**	H		63

3.1.2. Synthesis of pinane-based aminodiols

As mentioned in section 3.1, the starting material in the synthesis of pinane-type 3-amino-1,2-diols was enantiomerically pure (1*R*)-(-)-myrtenol **11**. The synthetic route included diastereoselective transformations as shown in Scheme 26.



Scheme 26

In the first instance, allylic alcohol **11** was transformed to allylic amine **125**. The well-known two-step synthesis involved the formation of acetimidate **124** in the presence of DBU.[113] The thermal rearrangement of **124** was induced by anhydrous K_2CO_3 under reflux in dry xylene via a chair-like transition (Figure 7). The transformation proved to be highly stereoselective, resulting in **125** as a single diasteroisomer. The nucleophilic attack of the acetonide group from the

pseudo-axial position is presumably more favorable than attack on the side of the dimethyl-substituted bridge. The relative configuration of the generated chiral center of acetamide **125** was well established by NMR, in accordance with literature data.[113]

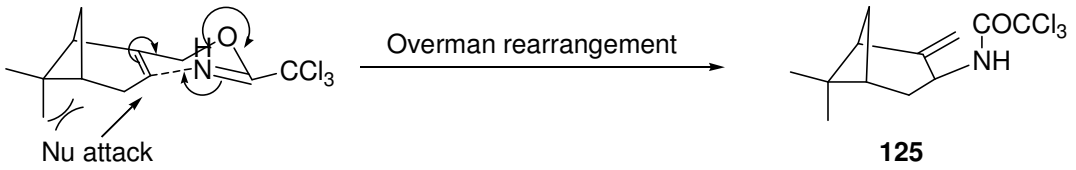


Figure 7

The double bond of **125** participated readily in dihydroxylation (Scheme 26). Use of $KMnO_4$ as an oxidizing agent in the presence of $MgSO_4$ or $BnEt_3NCl$ chloride as phase-transfer catalyst provided **126** as the only diastereoisomer detected in the crude reaction mixture. However, due to the low yield (10%), the isolation of **126** was unsuccessful and unreacted starting material was recovered. We therefore decided to utilize OsO_4-NMO as oxidizing system: excellent diastereoselectivity was found. The *syn*-selective addition of OsO_4 in the presence of the stoichiometric amount of the co-oxidant NMO furnished **126** in good yield (83%).

The formation of vicinal hydroxy functionalities on the same side of the acetamide group was sterically shielded, and the hydroxy and acetamide groups were therefore found to be in the *trans* position; the structure of **126** was confirmed by NOESY (Figure 8).

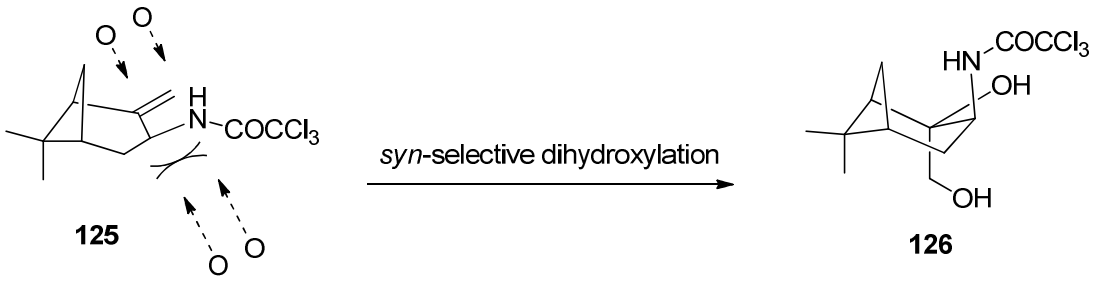
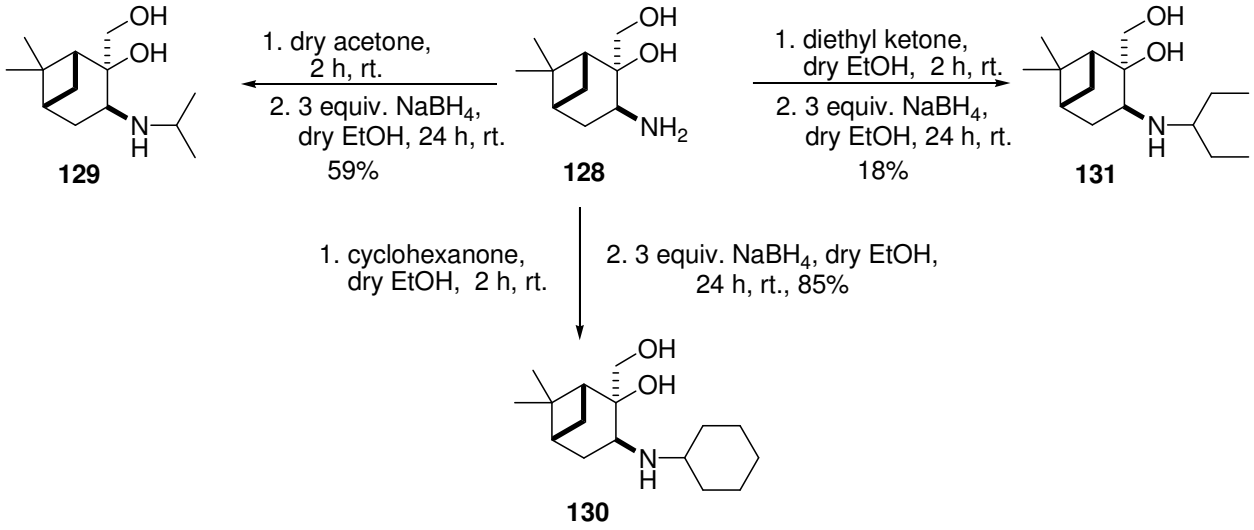


Figure 8

In order to achieve the target aminodiol structure, the protecting group had to be removed. There are several methods in the literature for cleavage of the trichloroacetamide group.[114-116] First we applied the reduction procedure with $NaBH_4$ in EtOH, but no transformation was found. In the next step, the deprotection was carried out with Cs_2CO_3, as base in DMF or DMSO. In both procedures, the preceding step was the protection of the hydroxy groups by converting into acetals with dry acetone in presence of PTSA. Unfortunately, none of the methods led to the

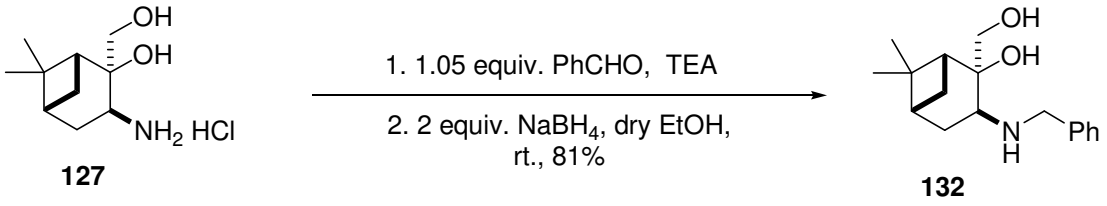
desired aminodiol. The key compound **127** was finally prepared by a convenient method: deprotecting **126** with 18% aqueous HCl solution at room temperature, during stirring for 24 hours, with 52% yield. Primary aminodiol **128** was readily liberated from its HCl salt (**127**) for further transformations (Scheme 26).

In order to extend the library of pinane-based 3-amino-1,2-diols, various *N*-substituted derivatives have been prepared. Primary aminodiol **128** was transformed to a secondary one by reductive *N*-alkylation as depicted in Scheme 27. The synthesis of **129** was carried out with dry acetone which served as solvent and reactant simultaneously. The Schiff base formed *in situ* was reduced with $NaBH_4$ in dry EtOH at room temperature. Secondary aminodiols **130** and **131** were prepared by stirring the reaction mixture with an excess of a ketone, such as cyclohexanone or diethyl ketone in dry EtOH, followed by reduction of the imines formed.



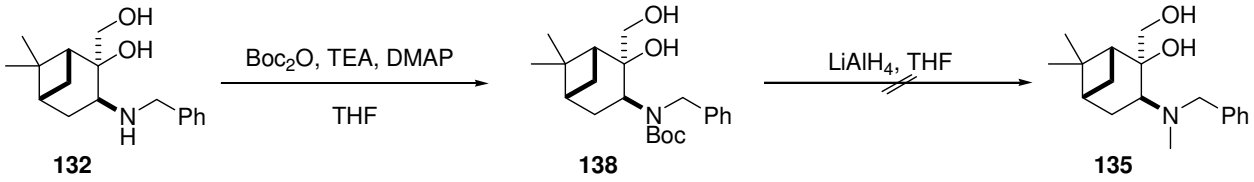
Scheme 27

Starting from **127**, different secondary and tertiary aminodiols were synthetized. Reductive alkylation with benzaldehyde in the presence of Et_3N provided *N*-benzyl derivative **132**.



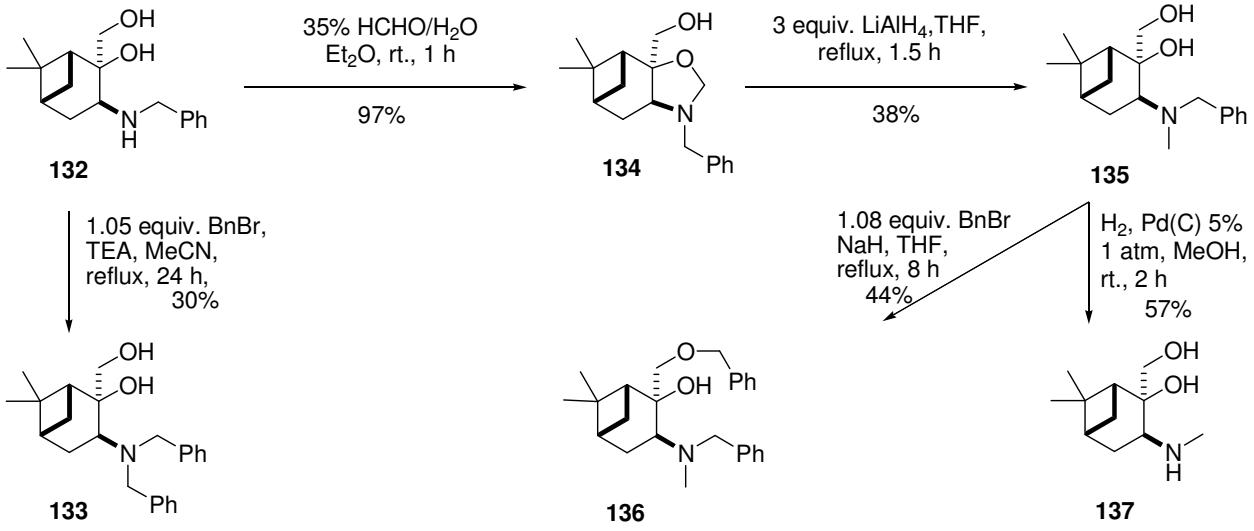
Scheme 28

In order to vary the substitution of the amino moiety, we attempted to synthetize the *N*-benzyl-*N*-methyl derivative. The first synthetic route applied included carbamate formation with Boc_2O, followed by $LiAlH_4$-mediated reduction. Unfortunately, monitoring of the reaction mixture with TLC revealed the conversion of **132** to **138** in low yield, probably due to the strong steric hindrance (Scheme 29).



Scheme 29

Therefore, an alternative pathway was chosen, as depicted in Scheme 30.

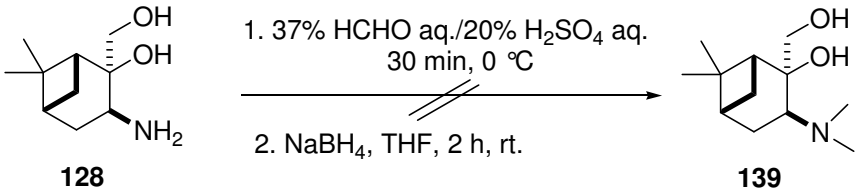


Scheme 30

The ring closure of **132** with formaldehyde furnished only pinane-fused oxazolidine **134** regioselectively, which underwent reduction with $LiAlH_4$ to result in *N*-benzyl-*N*-methyl derivative **135**. The steric hindrance on the N atom of **132** was increased by introducing an additional benzyl group with BnBr in MeCN in the presence of Et_3N. Probably due to the presence of the two bulky benzyl groups, tertiary aminodiol **133** was isolated in a moderate yield (30%). To incorporate the primary alcohol functional group into the ethereal function, **135** was subjected to *O*-alkylation with BnBr in THF in the presence of NaH, giving **136** in moderate

yield. Further transformation was made on the tertiary amino group: hydrogenolysis of **135** in the presence of Pd/C as catalyst led to *N*-methyl derivative **137** (Scheme 30).

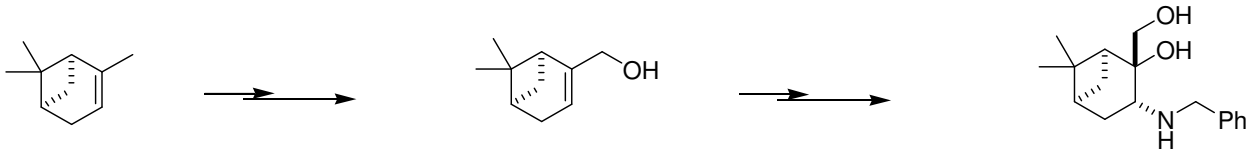
Our efforts to prepare *N*,*N*-dimethyl compound **139** according to a method described in literature[106] were unsuccessful (Scheme 31).



128 **139**

Scheme 31

The enantiomer of **132** was also synthetized. α-(+)-Pinene **140** was transformed to (1*S*)-(+)-myrtenol **141** in two steps, and **142** was prepared following the same reaction route as shown in Schemes 26 and 28 (Scheme 32, AnnexI).[113]



140 **141** **142**

Scheme 32

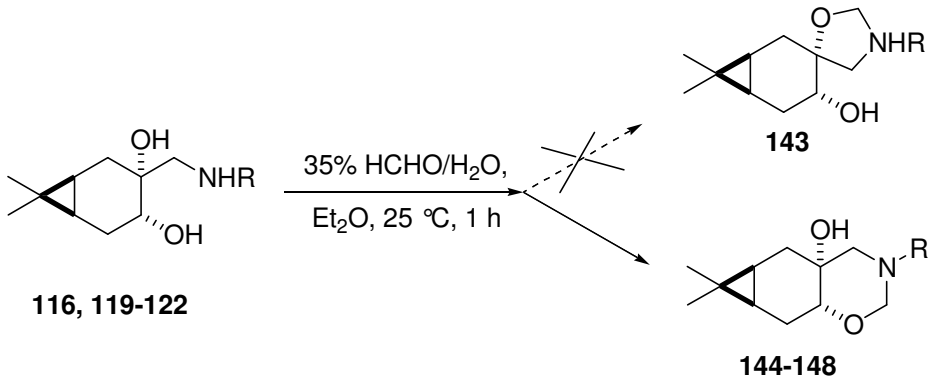
3.2. Synthesis of carane- and pinane-fused heterocycles

On the basis of earlier results achieved by our research group regarding the ring closure of monoterpene-based aminodiols (Scheme 8)[8,9] and the increased catalytic activity of *N*-containing heterocycles found by Andres *et al.*,[62] we investigated the cyclization tendencies of aminodiols **116**, **119**-**122**, **132** and **137** containing a secondary amino function.

With a 35% aqueous solution of formaldehyde as a convenient cyclization agent in both reaction pathways, two types of compound could be formed: the five-membered oxazolidine or the six-membered oxazine (Schemes 33 and 34).

Carane-based aminodiols **116** and **119**-**122** underwent ring closure, resulting exclusively in carene-fused 1,3-oxazines **144**-**148**. Incorporation of the secondary alcohol function in heterocyclic ring led to an extended tricyclic rigid structure, with a wide range of N atom

substituents. The preparation of 1,3-oxazine containing an unsubstituted N atom failed: only unseparable mixture of products was obtained.



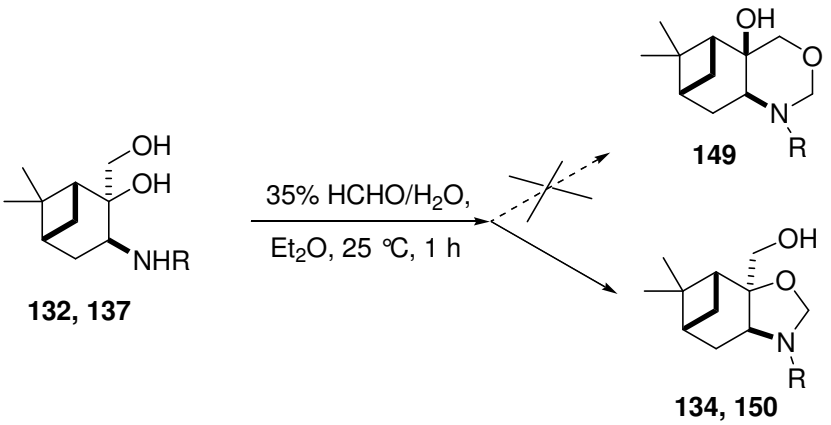
Scheme 33

The ring closure therefore proved highly regioselective, furnishing 1,3-oxazines in good yields (Table 2). No trace of spiro-oxazolidine derivative **143** was found (Scheme 33).

Table 2. Oxazines **144**-**148** obtained from cyclization of aminodiols **116** and **119**-**122**

Entry	Compound	R	Yield (%)
1	**144**	CH_2Ph	94
2	**145**	Me	84
3	**146**	CH(Me)Ph (*R*)	96
4	**147**	CH(Me)Ph (*S*)	81
5	**148**	*i*Pr	63

In the cases of pinane-based aminodiols containing a secondary amino function, reaction with formaldehyde could lead to the formation of pinane-fused oxazolidine or pinane-fused oxazine (Scheme 34). In the ring closures of **132** and **137**, regioisomers of previously reported pinane-based aminodiols,[8] pinane-fused oxazolidines **134** and **150**, were isolated as the only isomers. The ring-closure procedure was highly regioselective: the formation of 1,3-oxazines **149** was not detected.



Scheme 34

Table 3. Oxazolidines **134** and **150** obtained by cyclization of aminodiols **132** and **137**

Entry	Compound	R	Yield (%)
1	**134**	CH_2Ph	97
2	**150**	Me	41

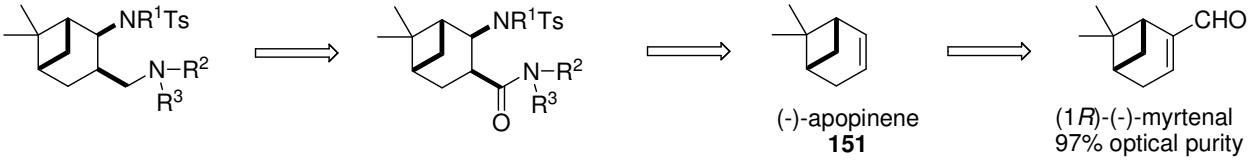
The rigid tricyclic system (**134** and **150**) obtained in this manner contains an incorporated tertiary alcohol group and a bulky *N*-benzyl (**134**) or a sterically less hindered *N*-methyl group (**150**), leaving the primary alcohol functionality unsubstituted (Table 3, Scheme 34). The ring closure of **128** bearing a primary amino group failed.

As compared with previous results,[8] where the regioselective ring closure of pinane-based aminodiols gave the spiro-fused oxazolidine (Scheme 8), the above-mentioned pinane-based aminodiols (**132** and **137**) furnished the five-membered heterocycles (**134** and **150**), fused with the pinane skeleton, with a free primary alcohol function. The formation of 1,3-oxazines (**144**-**148**) was preferred in the case of the carene-based aminodiols (**116**, **119**-**122**).

3.3. Synthesis of pinane-based bifunctionalized bidentate ligands

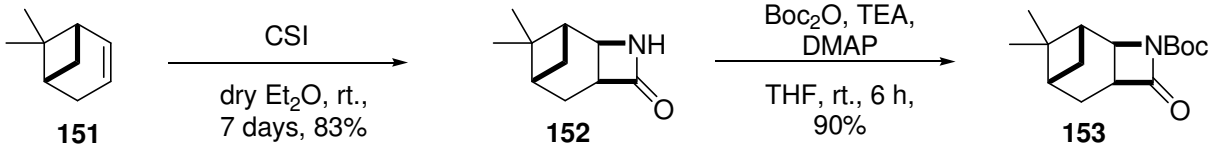
Pinane-type 1,3-amino amides and diamines were derived from (-)-apopinene, which was prepared from enantiomerically pure (1*R*)-(-)-myrtenal via literature methods (Scheme 35).[117,118] Former studies revealed the advantages of *apo* derivatives relative to α-pinene-based compounds, where the 2-methyl substituent attached next to the amino group increased the stability of the bicyclic pinane ring system and decreased the reactivity of the amino function.[10,11,46,45] Starting

from (-)-apopinene, therefore the disadvantageous steric effect of the 2-methyl substituent on the pinane skeleton was eliminated.



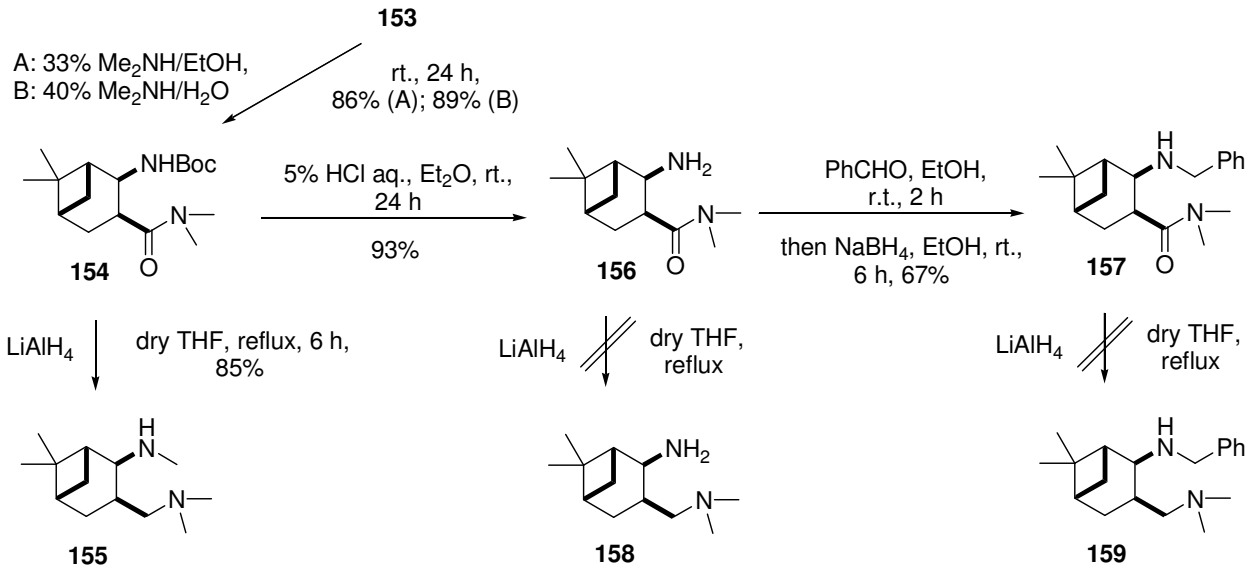
Scheme 35

A simple synthetic protocol for the preparation of β-amino acid derivatives, such as amino amides and diamines, consists in the transformation of β-lactams via ring opening. The highly regio- and stereospecific cycloaddition of CSI to enantiomerically pure (-)-apopinene **151** resulted in cyclic β-lactam **152**. The configuration of the only enantiomer **152** formed was confirmed by NMR and GC studies on the crude product. The carboxamide bond of the azetidinone was activated for further ring opening with di-*tert*-butyl dicarbonate, giving *N*-Boc β-lactam **153** in high yield.[117,119]



Scheme 36

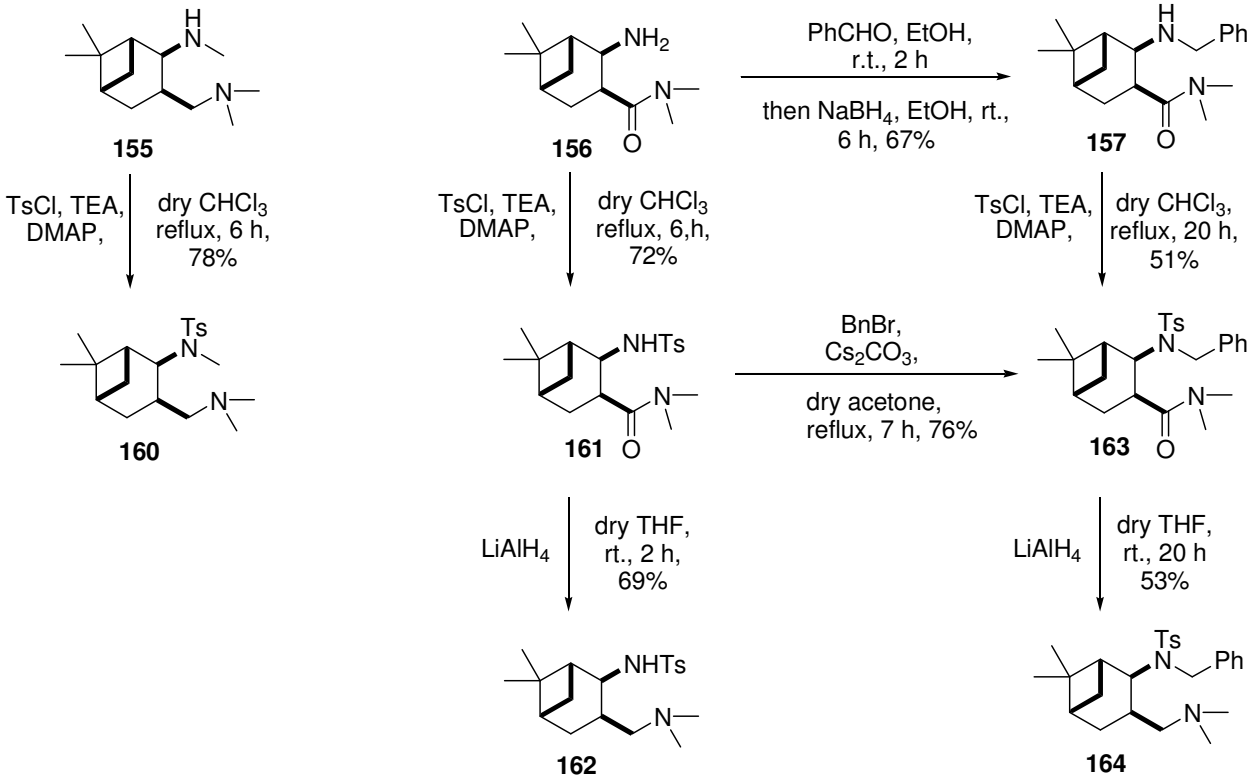
In order to build up the amino amide or diamine structure bearing the *N*,*N*-dimethyl group on the pinane skeleton, *N*-Boc β-lactam **153** was subjected to nucleophilic ring opening by Me_2NH in either aqueous or EtOH solution. Under both reaction conditions, optically pure *N*-Boc-protected amino amide **154** was obtained in good yield, which proved to be an efficient precursor for the synthesis of target molecules. The reduction of **154** by $LiAlH_4$ led to trimethyl-substituted diamine **155**. Deprotection of **154** furnished derivative **156** bearing a primary amino function. In order to increase the steric hindrance on the amino function, **156** was converted to *N*-benzyl amino amide **157** via reductive alkylation. Unfortunately, reduction of **156** and **157** with $LiAlH_4$ in order to achieve 1,3-diamines **158** and **159** containing a primary amino or an *N*-benzyl amino group failed, and therefore an alternative synthetic pathway was devised (Scheme 37).



Scheme 37

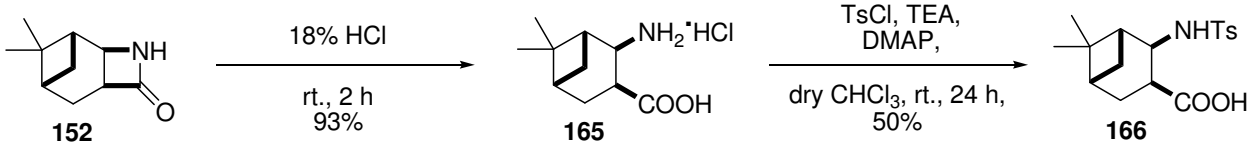
Diamine **155** and amino amides **156** and **157**, containing an *N*-methyl, a primary amino and a bulky *N*-benzyl group, were extended toward the synthesis of tosylated derivatives. Preparation of **160** was achieved by the addition of tosyl chloride in the presence of TEA and DMAP as catalyst under refluxing in dry $CHCl_3$. Tosylated amino amides **161** and **163** were prepared by an analogous method. Two different synthetic routes led to **163**, as depicted in Scheme 38. In the first instance, reductive amination of **156** followed by tosylation gave **163** in moderate yield (51%), probably due to the unfavored steric hindrance of the *N*-benzyl group. A higher yield (76%) was achieved when consecutive tosylation and *N*-alkylation were performed. With NaH as base in the alkylation procedure, no reaction was observed, but the use of Cs_2CO_3 proved to be effective in the synthesis of **163**. Reduction of amino amides **161** and **163** with $LiAlH_4$ furnished 1,3-diamines **162** and **164** in moderate to good yields.

In order to extend the library of amino amides and diamines we followed the above-mentioned ring-opening procedure (Scheme 37), choosing Et_2NH as the nucleophilic partner. Despite our expectations, an inseparable mixture of amine-type compounds was formed. When β-lactam **153** was reacted with Et_2NH in the presence of a catalytic amount of LiOH to facilitate the opening of azetidinone,[10,120] a decomposed reaction mixture was obtained.



Scheme 38

An alternative pathway was therefore chosen for the preparation of variously substituted amino amides and 1,3-diamines, starting from optically active β-amino acid derivative **166**. The key intermediate β-amino acid hydrochloride **165** was prepared by the hydrolysis of **152** with 18% aqueous HCl solution, following a literature method.[117] Treatment of **165** with tosyl chloride afforded *N*-tosyl β-amino acid **166** in moderate yield.



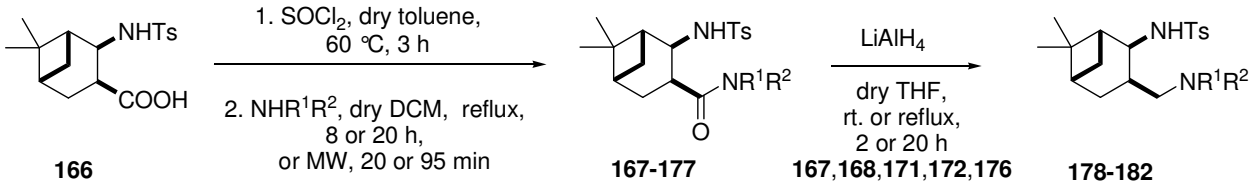
Scheme 39

Conversion of the carboxylic group into amide was achieved via acid chloride followed by subsequent substitution by various primary and secondary amines. Amino amides **167**-**171** and **173**-**176** were synthetized under reflux conditions. Microwave activation was necessary for the amidation of **166** with *N*-methyl-*N*-phenylamine and aniline. In the case of **170**, NH_3 gas was introduced into the reaction mixture. The reaction of **166** with both enantiomers of α-

methylbenzylamine introduced new chiral centers into the structures of **173** and **174**. Our efforts to increase the steric hindrance of the amide through the reaction of **166** with 2,2,6,6-tetramethylpiperidine failed.

A library of optically active pinane-based amino amides was built up, consisting of compounds with a diversely substituted amide functionality.

In order to obtain 1,3-diamines, the next synthetic step involved the $LiAlH_4$-mediated reduction of *N*-tosyl amino amides **167**-**177**.



166 **167-177** **167**,**168**,**171**,**172**,**176** **178-182**

Scheme 40

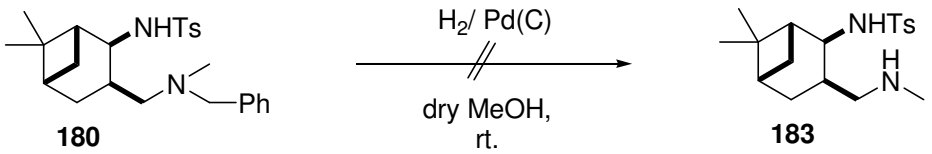
The synthesis of 1,3-diamines bearing a tertiary amino function took place with good yields, the reaction conditions varying from room temperature to reflux, with a reaction time of from 2 hours to 20 hours, as summarized in Table 4.

Table 4. Pinane-based amino amides **167**-**177** and 1,3-diamines **178**-**182**

Entry	Compound		R^1	R^2	Yield (%)	
	β-amino amides	1,3-diamines			β-amino amides 167-177	1,3-diamines 178-182
1	**167**	**178**	Et	Et	66	80
2	**168**	**179**		$-(CH_2)_4-$	72	78
3	**169**		H	CH_2Ph	85	
4	**170**		H	H	66	
5	**171**	**180**	Me	CH_2Ph	87	60
6	**172**	**181**	Me	Ph	69	41
7	**173**		H	CH(Me)Ph (*R*)	78	
8	**174**		H	CH(Me)Ph (*S*)	85	
9	**175**		H	Me	90	
10	**176**	**182**		$-(CH_2)_5-$	89	78
11	**177**		H	Ph	40	

The preparation of diamines containing a primary or a secondary amino group by reduction of the corresponding amides failed. Treatment of **169**, **170**, **173**-**175** and **177** with $LiAlH_4$ led to inseparable amine-type products

We attempted to apply a different strategy for the synthesis of tosylated 1,3-diamine bearing a secondary amino group by the hydrogenolysis of the readily prepared *N*-benzyl derivative **180**, but *N*-methyl derivative **183** could not be isolated (Scheme 41).



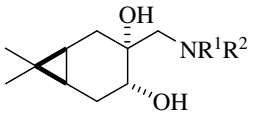
Scheme 41

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

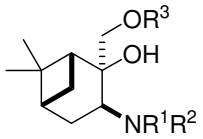
Enantioselective addition of organozinc reagents to prochiral aldehydes is the most studied and effective C-C-bond formation reaction and the most frequent classical test for screening effective chiral promotors for these processes. Asymmetric addition of Et_2Zn to aldehyde was the model reaction chosen. In comparison with Me_2Zn, where reduced reactivity was found,[121] or Ph_2Zn, where a competitive uncatalyzed side-reaction occurred, the catalyzed alkylation of benzaldehyde by Et_2Zn [122] required mild reaction conditions: generally room temperature, 20 h and an Ar atmosphere.

The enantioinduction of a chiral catalyst on the formation of the optically active secondary alcohols can be influenced by structural factors such as the absolute configuration, coordination groups, steric hindrance or the ligand skeleton.

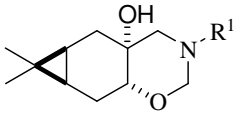
In order to establish the efficiency of the monoterpene-based bi- or tridentate chiral ligands prepared (Figure 9), we evaluated them in the enantioselective addition of Et_2Zn to benzaldehyde (Scheme 42).



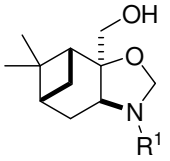
114: R^1 = Me, R^2 = CH_2Ph; **115**: R^1 = R^2 = CH_2Ph;
116: R^1 = H, R^2 = CH_2Ph; **117**: R^1 = CH_2Ph, R^2 = CH(Me)Ph (*R*);
118: R^1 = CH_2Ph, R^2 = CH(Me)Ph (*S*);
119: R^1 = H, R^2 = CH(Me)Ph (*R*);
120: R^1 = H, R^2 = CH(Me)Ph (*S*);**121**: R^1 = H, R^2 = *i*-Pr;
122: R^1 = H, R^2 = Me; **123:** R^1 = R^2 = H



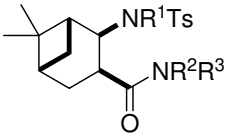
128: R^1 = R^2 = R^3 = H; **129**: R^1R^2 = *i*-Pr;
130: R^1R^2 = cyclohexyl; **131**: R^1R^2 = $(CH)Et_2$;
132: R^1 = R^3 = H, R^2 = CH_2Ph;
133: R^1 = R^2 = CH_2Ph, R^3 = H;
135: R^2 = Me, R^3 = CH_2Ph, R^3 = H;
136: R^1 = R^3 = CH_2Ph, R^2 = Me; **137**: R^1 = R^3 = H, R^2 = Me



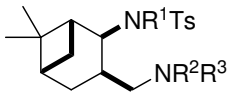
144: R^1 = CH_2Ph; **145**: R^1 = Me;
146: R^1 = CH(Me)Ph (*R*);
147: R^1 = CH(Me)Ph (*S*);
148: R^1 = *i*-Pr



134: R^1 = CH_2Ph; **150**: R^1 = Me



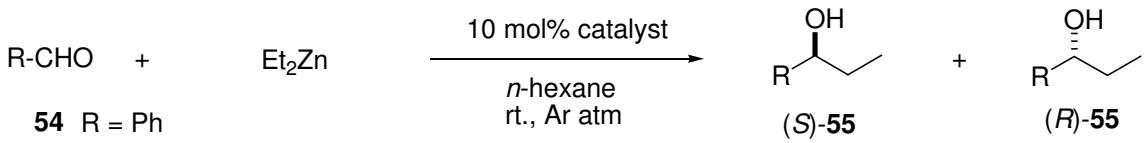
161: R^1 = H, R^2 = R^3 = Me; **163**: R^1 = CH_2Ph, R^2 = R^3 = Me;
167: R^1 = H, R^2 = R^3 = Et; **168**: R^1 = H, R^2R^3 = $(CH_2)_4$;
169: R^1 = R^2 = H, R^3 = CH_2Ph; **170**: R^1 = R^2 = R^3 = H;
171: R^1 = H, R^2 = Me, R^3 = CH_2Ph;
172: R^1 = H, R^2 = Me, R^3 = Ph;
173: R^1 = R^2 = H, R^3 = CH(Me)Ph (*R*);
174: R^1 = R^2 = H, R^3 = CH(Me)Ph (*S*);
175: R^1 = R^2 = H, R^3 = Me;
176: R^1 = H, R^2R^3 = $(CH_2)_5$; **177**: R^1 = R^2 = H, R^3 = Ph



160: R^1 = R^2 = R^3 = Me; **162**: R^1 = H, R^2 = R^3 = Me;
164: R^1 = CH_2Ph, R^2 = R^3 = Me; **178**: R^1 = H, R^2 = R^3 = Et;
179: R^1 = H, R^2R^3 = $(CH_2)_4$;
180: R^1 = H, R^2 = Me, R^3 = CH_2Ph;
181: R^1 = H, R^2 = Me, R^3 = Ph; **182**: R^1 = H, R^2R^3 = $(CH_2)_5$;

Figure 9

The reaction was performed at room temperature under an Ar atmosphere. In the first instance, 1M Et_2Zn in *n*-hexane solution was added to the respective catalyst (0.1 mmol) and stirred for 25 min. Benzaldehyde (1 mmol) was then added to the reaction mixture with subsequent stirring at room temperature for a further 20 h. After the work-up, the crude product was purified by flash column chromatography (*n*-hexane/EtOAc = 4:1). The *ee* and absolute configuration of the resulting alcohols were determined by chiral GC, using a chiral stationary phase (Chirasil-Dex CB column) according to literature methods.[45] Our results are presented in Tables 5-10.



54 R = Ph

(*S*)-**55**

(*R*)-**55**

Scheme 42

When the amount of the catalyst was reduced to 5 mol%, lower enantioselectivity was observed. Furthermore, when the test reaction was carried out at decreased temperature (4 °C), no improvement in enantioinduction was achieved.

3.4.1. Application of tridentate monoterpene-based aminodiols in enantioselective alkylation of benzaldehyde

To explore the efficiency of tridentate ligands, a library of chiral carane- and pinane-based aminodiols were applied as catalysts in the above-mentioned model reaction (Scheme 42).
The results obtained with carane-based 3-amino-1,2-diols **114**-**123** are presented in Table 5.

Table 5. Addition of Et_2Zn to benzaldehyde, catalyzed by carane-based aminodiols **114**-**123**

Entry	Catalyst (10 mol%)	Yield[a] (%)	*ee*[b] (%)	Configuration of major product[c]
1	**114**	87	13	*R*
2	**115**	84	10	*S*
3	**116**	90	3	*S*
4	**117**	75	31	*R*
5	**118**	80	8	*S*
6	**119**	88	7	*S*
7	**120**	78	37	*R*
8	**121**	73	30	*R*
9	**122**	81	16	*S*
10	**123**	73	5	*S*

[a]Yields after silica column chromatography are given. [b]Determined on the crude product by GC (Chirasil-DEX CB column). [c]Determined by comparing the t_R of the GC analysis and the optical rotation with the literature data.[45]

However, low to moderate enantioselectivities were found, preventing the acquisition of valuable information regarding the *N*-substitution and enantioinduction correlation. Significantly lower enantioselectivities were observed in cases of *S* selectivity (applying catalysts **115**, **116**, **118**, **119**,

122 and **123**) than those involving *R* selectivity (catalysts **114**, **117**, **120** and **121**). Aminodiol **120** with an *N*-(*S*)-1-phenylethyl substituent proved to be the best catalyst among the carane-based aminodiols, but still with only moderate enantioselectivity.

Pinane-based tridentate ligands were also tested as catalysts in the model reaction. The results obtained are summarized in Table 6.

Table 6. Addition of Et_2Zn to benzaldehyde catalyzed by pinane-based aminodiols **128**-**133**, **135**-**137** and **142**

Entry	Catalyst (10 mol%)	Yield[a] (%)	*ee*[b] (%)	Configuration of major product[c]
1	**128**	83	1	*R*
2	**129**	79	40	*R*
3	**130**	76	19	*R*
4	**131**	81	3	*R*
5	**132**	85	61	*R*
6	**133**	80	1	*R*
7	**135**	73	26	*R*
8	**136**	86	6	*R*
9	**137**	82	1	*R*
10	**142**	83	39	*S*

[a]Yields after silica column chromatography are given. [b]Determined on the crude product by GC (Chirasil-DEX CB column). [c]Determined by comparing the t_R of the GC analysis and the optical rotation with the literature data[45]

Weak catalytic activity was observed with chiral ligands **128**, **131**, **133** and **137**. Whit catalysts **129**, **130** and **135**, increased enantioselectivity was achieved. *N*-Benzyl derivative **132** displayed the greatest enantioinduction, yielding (*R*)-**55** with 61% *ee*. To clarify the observed *N*-substituent-dependent enantioinduction, quantum chemical molecular modeling was performed for the Noyori-type μ-oxo transition states of aminodiol **132**.[123] The results were in good accordance with the experimentally observed selectivity for **132**. The catalytic activity of **142**, an enantiomer of the best catalyst **132**, was also examined, but low enantioinduction was observed, yielding the expected *S* secondary alcohol (*S*)-**55** (Table 6, Entry 10). When *O*-alkylated **136** was tested in the model reaction, a low *ee* value was observed. Pinane-based aminodiols **128**-**137** led to the formation of the *R* enantiomeric product (*R*)-**55**. Ligands bearing a secondary amino function exhibited a better catalytic effect; the substituent-dependent enantioselectivity was observed in

the sequence NH_2 < NRR < NHR. Tridentate pinane-based aminodiols **128**, **129** and **132-137** are regioisomers of those reported earlier,[8] where opposite selectivity was observed, affording (*S*)-1-phenylpropanol (*S*)-**55**, the catalytic activity increasing in the sequence NH_2 < NHR < NRR.

From a comparison of the catalytic activities of the carane-based and pinane-based tridentate ligands, it is obvious that the latter exert a greater influence on the enantioselectivity in the asymmetric alkylation of benzaldehyde than do the carane-based species, probably because of the rigidity and greater steric hindrance of the pinane bicyclic structure.

Table 7. Comparison of the best carane- and pinane-based aminodiol catalysts in the enantioselective alkylation of benzaldehyde

Catalyst (10 mol%)	***ee* (%)**	**Configuration of major product[c]**	**Catalyst (10 mol%)**	***ee* (%)**	**Configuration of major product[c]**
120	37	*R*	**132**	61	*R*
117	31	*R*	**129**	40	*R*
121	30	*R*	**135**	26	*R*

The relevant observation regarding the best tridentate monoterpene-based catalysts (**117**, **120**, **121**, **129**, **132** and **135**) was that aromatic substitution on the amino function was necessary for optimal results; this is probably due to the л-л overlapping of the phenyl ring of the catalysts and benzaldehyde.

3.4.2. Application of monoterpene-based heterocycles in enantioselective alkylation of benzaldehyde

The carane-based 1,3-oxazines and pinane-based oxazolidines **144-148**, **134** and **150** were tested as catalysts in the addition of Et_2Zn to benzaldehyde (Table 8). In accordance with our expectations, 1,3-oxazines promoted the model reaction with excellent enantioselectivity. The extended tricyclic system in 1,3-oxazines condensed with a carane moiety proved to be an adequate structure for the best discrimination of the two enantiotopic faces of benzaldehyde. Ligands bearing substituents with an extra asymmetric center **146** and **147** showed significant differences in their catalytic activity (*ee* = 96% and *ee* = 62%). The best *ee* value (*ee* = 96%) was obtained with *N*-(*R*)-1-phenylethyl-substituted 1,3-oxazine **146**. When catalyst **148** with a less

steric congested *i*-propyl group was used, a decrease in asymmetric induction was observed. For ligands **144**-**148** formation of (*S*)-1-phenylpropanol (*S*)-**55** was preferred.

The enantioinduction exerted in the aforementioned model reaction by pinane-fused oxazolidine **134** and **150** was low, giving (*R*)-**55** as the major product.

Table 8. Carane- and pinane-based heterocycles as catalysts in enantioselective alkylation of benzaldehyde

Entry	Catalyst (10 mol%)	Yield[a] (%)	*ee*[b] (%)	Configuration[c]
1	**144**	74	94	*S*
2	**145**	72	92	*S*
3	**146**	77	96	*S*
4	**147**	71	62	*S*
5	**148**	83	38	*S*
6	**134**	75	27	*R*
7	**150**	77	8	*R*

[a]Yields after silica column chromatography are given. [b]Determined on the crude product by GC (Chirasil-DEX CB column). [c]Determined by comparing the t_R of the GC analysis and the optical rotation with the literature data.[45]

An excellent improvement in enantioselectivity was achieved with carane-fused 1,3-oxazines, can presumably be attributed to their conformationally more constrained structure. However, the rigid tricyclic ring system with high steric congestion in pinane-based oxazolidines influenced the catalytic activity only weakly. In order to account for the enantioselectivity observed with 1,3-oxazines, a presumed transition state was proposed for catalyst **144**. The *si*-face attack of the ethyl group on benzaldehyde provided the *S* enantiomer of the secondary alcohol (Figure 10).

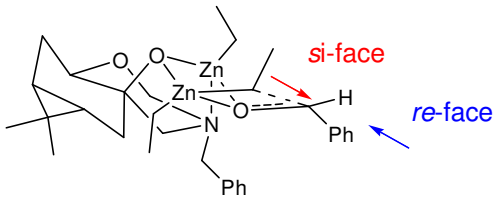


Figure 10

Thus, carane-fused 1,3-oxazines **144**-**148** could be considered efficient asymmetric catalysts, affording the highest *ee* and good chemical yields in the model reaction (Scheme 42, Table 8).

3.4.3. Application of bidentate pinane-based chiral ligands in enantioselective alkylation of benzaldehyde

To explore the catalytic ability of pinane-based bifunctionalized chiral ligands, β-amino amides, **167**-**177** and 1,3-diamines **161**, **163** and **178**-**182** were applied in the model reaction presented in Scheme 42. The results obtained are given in Table 9.

In first instance, tosylated β-amino amides **161** and **163** and then 1,3-diamines **160**, **162** and **164** were tested. Variation of the substituents on the tosylated amino function at position C-2 of compounds bearing the *N*,*N*-dimethylamide (**161** and **163)** or *N*,*N*-dimethylaminomethylene group (**160**, **162** and **164)** allowed a crude insight into the substitution-dependent catalytic effect of these ligands. However, low to moderate enantioselectivities were observed. The presence of a methyl or even a bulkier benzyl group on the amino function at position C-2 lowered the enantioinduction. Higher *ee* values were achieved with catalysts **161** and **162** with an unsubstituted tosylated amino group.

These results, together with literature data,[106] led us to conclude that the acidic proton of the sulfonamide nitrogen was responsible for a reasonable level of catalytic activity. Catalysts **160**-**164** provided (*R*)-1-phenyl-1-propanol (*R*)-**55** as the major enantiomer (Table 9).

Taking these experimental findings into account, we continued to explore the influence of substituents on the amide or amino group at position C-3 by applying chiral ligands **167**-**182**.

Catalyst **170** with a primary amide group furnished low *ee* values, probably due to the lack of steric hindrance, while ligands **167**, **168**, **171**, and **172** bearing a tertiary amide function slightly improved the enantioselectivity. A higher *ee* was achieved with *N*-phenyl-*N*-methyl derivative **172** (*ee* = 65%). Preference for the formation of (*R*)-1-phenylpropanol was observed with β-amino amides **167**, **168**, and **170**-**172** containing a primary or tertiary amide group. When 1,3-diamines **178**-**182** were tested as catalyst, low chiral induction was observed, yielding the *R* secondary alcohol (*R*)-**55**.

β-Amino amides bearing a secondary amide group were successfully applied in the aforementioned test reaction (Scheme 42). The highest *ee* value (*ee* = 83%) was achieved with *N*-phenyl derivative **177**. Catalyst **169** with *N*-benzyl and **175** with *N*-methyl substitution provided

76% and 63% *ee*. The introduction of a new asymmetric center by using (*R*)- and (*S*)-1-phenylethyl-substituted derivatives **173** and **174** led to unsatisfactory results, presumably because of the high steric hindrance. Chiral β-amino amides containing a secondary amide function gave (*S*)-**55** as the main product.

The switching of enantioselectivity was a consequence of the variation of the substituents on the amide function.

To the best of our knowledge, this is the first example of the application of β-amino amides as catalysts in the asymmetric addition of Et_2Zn to aldehydes.

Table 9. Addition of Et_2Zn to benzaldehyde, catalyzed by various types of 1,3-diamines and β-amino amides.

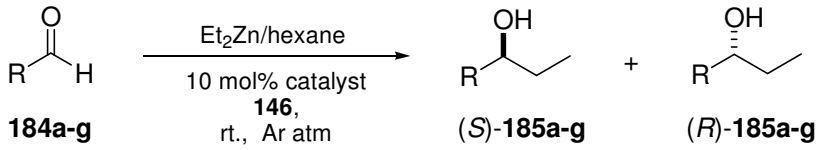
Entry	Catalyst (10 mol%)		Yield[a] (%)	*ee*[b] (%)	Configuration of major product[c]
	β-amino amides	1,3-diamines			
1		**160**	89	5	*R*
2	**161**		90	35	*R*
3		**162**	81	38	*R*
4	**163**		83	6	*R*
5		**164**	88	8	*R*
6	**167**		79	48	*R*
7	**168**		82	30	*R*
8	**169**		80	76	*S*
9	**170**		93	27	*R*
10	**171**		77	32	*R*
11	**172**		75	65	*R*
12	**173**		80	23	*R*
13	**174**		86	14	*S*
14	**175**		75	63	*S*
15	**176**		78	36	*R*
16	**177**		90	**83**	*S*
17		**178**	85	29	*R*
18		**179**	92	6	*S*
19		**180**	74	26	*R*
20		**181**	70	10	*R*
21		**182**	72	5	*R*

[a]Yields after silica column chromatography. [b]Determined on the crude product by GC (Chirasil-DEX CB column). [c]Determined by comparing the GC analysis t_R and the optical rotation with the literature data.[45]

3.4.4. Extension of the asymmetric alkylation reaction

The investigation of the catalytic activity of monoterpene-based chiral ligands in the asymmetric alkylation of benzaldehyde prompted us to examine their possible applicability for other asymmetric transformations. We therefore extended the model reaction by applying various

aromatic and aliphatic aldehydes in the enantioselective Et_2Zn addition reaction. The best catalyst **146** was chosen from the library of chiral ligands prepared, and was evaluated in the test reaction depicted in Scheme 43. The enantiomeric purities of the 1-aryl and 1-alkyl-1-propanols obtained were determined by GC on a CHIRASIL-DEX CB column or by chiral HPLC analysis on a Chiralcel OD-H column, according to literature methods.[12,43,45,62,103,124-126,]



184a-g (*S*)-**185a-g** (*R*)-**185a-g**

Scheme 43

Table 10. Addition of Et_2Zn to aldehydes catalyzed by ligand **146**.

Entry	Product	R	Yield[a] (%)	*ee* (%)[b]	Configuration of major product[c]
1	**185a**	4-$MeOC_6H_4$	89	97	*S*
2	**185b**	4-MeC_6H_4	93	97	*S*
3	**185c**	3-$MeOC_6H_4$	91	96	*S*
4	**185d**	3-MeC_6H_4	90	93	*S*
5	**185e**	2-naphthyl	86	96	*S*
6	**185f**	cyclohexyl	80	92	*S*
7	**185g**	*n*-butyl	87	77	*S*

[a]Yields after silica column chromatography are given. [b]Determined on the crude product by HPLC (Chiracel OD-H). [c]Determined by comparing the t_R of the HPLC analysis and the optical rotation with the literature data.[12,43,45,62,103,124-126]

From the results presented in Table 10, it clearly followed that 1,3-oxazine **146** was an efficient catalyst in asymmetric transformation (Scheme 43). High chemical yields and excellent *ee* values were obtained in the addition of Et_2Zn to variously substituted aromatic aldehydes catalyzed by 1,3-oxazine **146**, while lower, but still good yields and selectivities were achieved when aliphatic aldehydes were applied. The major enantiomer in all cases (Table 10) was the (*S*)-alcohol (*S*)-**185a-g**.

4. Summary

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.

Functionalization of the enantiomeric monoterpenes (**11**, **60**, **140** and **151**) was achieved by applying simple synthetic steps, including stereoselective transformations.

The optical purity of (1*S*)-(+)-3-carene **60** remained intact in further reactions; the formation of the new asymmetric centers was controlled by stereoselective steps. Novel, optically active epoxy alcohol **111** was subjected to a stereoselective epoxide ring-opening procedure, resulting in variously substituted aminodiols. Carane-based aminodiols **114**-**123** were prepared with moderate to good overall yields.

Transformation of readily available (1*R*)-(-)-myrtenol **11** by well-known methods resulted in enantiopure key intermediate **127** in good yield, a corresponding precursor for optically active pinane-based aminodiols **128**-**133** and **135**-**137**. Analogously, pinane-based aminodiol **142**, an enantiomer of **132**, was successfully prepared by using a similar synthetic protocol to that for **132**.

The ringclosure of pinane- and carane-based aminodiols proved to be highly regioselective, furnishing exclusively carane-fused 1,3-oxazines **144**-**148** and pinane-fused oxazolidines **134** and **150**. Formation of regioisomer carane-based spiroderivative **143** or pinane-based six-membered heterocycle **149** was not observed.

Simple synthetic procedures for the synthesis of enantiomerically pure pinane-based β-lactams **152** and Boc-protected **153** involved regio- and stereoselective CSI addition to enantiopure apopinene **151**. The optically active β-amino amides and 1,3-diamines were derived from **152** and **153**. The consecutive lactam-opening procedure and tosylation reaction furnished amino amides **161**, **163** and **167**-**177**. By subsequent reduction, only diamines bearing a tertiary amino function (**160**, **162**, **164** and **178**-**182**) could be synthetized, and hence a series of variously substituted β-amino acid derivatives were prepared.

The 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.

Carane-based tridentate catalysts **114**-**123** exerted low enantioinduction in the asymmetric addition of Et_2Zn to benzaldehyde, affording the *R* or the *S* enantiomer of 1-phenyl-1-propanol **55**. A moderate *ee* value (*ee* = 37%) was achieved by utilizing *N*-(*S*)-1-phenylethyl derivative **120**.

In comparison, improved catalytic activity was observed with pinane-based tridentate ligands **128**-**133** and **135**-**137**, yielding (*R*)-**55**. *N*-Benzyl aminodiol **132** 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 sequence NH_2 < NRR < NHR. The catalytic activity of enantiomer **142** was weaker (*ee* = 39%) yielding (*S*)-**55**.

Carane-condensed 1,3-oxazines **144**-**148** proved to be excellent catalysts in the addition of Et_2Zn to benzaldehyde, furnishing (*S*)-**55** with high *ee* values (*ee* value up to 96%). The best carane-based tricyclic catalyst was (*R*)-1-phenylethyl-substituted oxazine **146**.

In contrast, pinane-fused oxazolidines **134** and **150** displayed low chiral induction, with the formation of (*R*)-**55** as the major enantiomer.

The pinane-based bidentate ligands **160**-**164** and **167**-**182** provided moderate to good asymmetric induction in model reactions. Depending upon the degree of *N*-substitution of β-amino acid derivatives, switching of the enantioselectivity was observed. With β-amino amides containing a primary or tertiary amide group **161**, **163**, **167**, **168**, **170**-**172** and **174** and 1,3-diamines **160**, **162**, **164** and **178**-**182**, moderate *ee* values was achieved, giving (*R*)-**55** as the major product. β-Amino amides with a secondary amide function **169**, **173**-**175** and **177** improved the enantioselectivity, providing (*S*)-**55**. The highest *ee* value (*ee* = 83%) was observed by applying β-amino amide **177**. To the best of our knowledge, this is the first preparation of β-amino amides as suitable catalysts in the addition of Et_2Zn to benzaldehyde.

The efficiency of carane-fused 1,3-oxazine **146** was tested in an extended model reaction, giving both the highest yields and enantioselectivities up to 97% *ee* with *S* selectivity.

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ANNEX I

The 1*S*,5*S*,3*R*,5*S* enantiomer of **127 w**as prepared as described above; $[\alpha]_D^{20}$ = -12.0 (*c* = 0.125, MeOH); the spectroscopic data and mp were similar to those for **127**. Analysis found: C, 43.44%; H, 5.37%; Cl, 32.28%; N, 4.17%.

The 1*S*,5*S*,3*R*,5*S* enantiomer of **128 w**as prepared as described above; $[\alpha]_D^{20}$ = +9.0 (*c* = 0.125, MeOH); the spectroscopic data and mp were similar to those for **128**. Analysis found: C, 54.33%; H, 9.14%; N, 6.25%, Cl, 15.69%.

The 1*S*,5*S*,3*R*,5*S* enantiomer of **132** was prepared as described above; $[\alpha]_D^{20}$ = -5.0 (*c* = 0.125, MeOH); the spectroscopic data and mp were similar to those for **132**. Analysis found: C, 73.77 H, 9.02% N, 5.40%.