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Synthesis and Investigation of Pinane-Based Chiral Tridentate Ligands in the Asymmetric Addition of Diethylzinc to Aldehydes

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Abstract: A library of pinane-based chiral aminodiols, derived from natural (–)-*β*-pinene, were prepared and applied as chiral catalysts in the addition of diethylzinc to aldehydes. (–)-*β*-Pinene was reacted to provide 3-methylenenopinone, followed by a reduction of the carbonyl function to give a key allylic alcohol intermediate. Stereoselective epoxidation of the latter and subsequent ring opening of the resulting oxirane with primary and secondary amines afforded aminodiols. The regioselectivity of the ring closure of the *N*-substituted secondary aminodiols with formaldehyde was examined and exclusive formation of oxazolidines was observed. Treatment of the allylic alcohol with benzyl bromide provided the corresponding *O*-benzyl derivative, which was transformed into *O*-benzyl aminodiols by aminolysis. Ring closure of the *N*-isopropyl aminodiol derivative with formaldehyde resulted in spirooxazolidine. The obtained potential catalysts were applied in the reaction of both aromatic and aliphatic aldehydes to diethylzinc providing moderate to good enantioselectivities (up to 87% *ee*). Through the use of molecular modeling at an ab initio level, this phenomenon was interpreted in terms of competing reaction pathways. Molecular modeling at the RHF/LANL2DZ level of theory was successfully applied for interpretation of the stereochemical outcome of the reactions leading to display excellent (*R*) enantioselectivity in the examined transformation.

Keywords: (–)-*β*-pinene; 3-methylenenopinone, aminodiols; diethylzinc, chiral catalyst

1. Introduction

Chiral synthons, applied successfully in asymmetric homogenous and heterogeneous catalysis, have achieved increasing importance in organic chemistry in recent years [1–3]. The enantioselective addition of dialkylzinc to aldehydes catalyzed by different types of chiral ligands has been investigated intensively [4–6], because the preparation of enantiomerically pure or enriched alcohols is of considerable interest for the synthesis of bioactive compounds [7–9] and natural products [10,11].

Aromatic and aliphatic aminodiols bearing a 1,2- or a 1,3-aminoalcohol moiety have proven to be highly efficient building blocks [12–15]. They have been applied as starting materials in the stereoselective synthesis of compounds of pharmacological interest, including 1,3-oxazines [16], 1,3-thiazines [17–19] and 2-iminothiazolidines [20]. In addition to their synthetic importance, aminodiols can also be applied as chiral ligands and auxiliaries in enantioselective transformations [21–24] including intramolecular radical cyclizations [25], intramolecular [2+2] photocycloaddition [26] and Grignard addition [27,28]. Therefore, it is not surprising that the preparation of new chiral aminodiols has been a topic of increased interest. Although numerous enantiopure chelating ligands have been

prepared [29–34], there is still a need for new types obtainable by concise syntheses from inexpensive starting materials.

Naturally occurring chiral monoterpenes such as (+)- and (–)-*α*-pinene [21,35,36], (+)-carene [37,38], (+)-camphor [31,39], (–)-menthone [34], (–)-fenchone [29], (+)-sabinol [40], (–)-myternol [21,41], (–)-pulegone [42], neoisopulegol [43] and (*S*)-perillyl alcohol [44] have been widely used as key intermediates for the synthesis of chiral catalysts and auxiliaries for asymmetric synthesis.

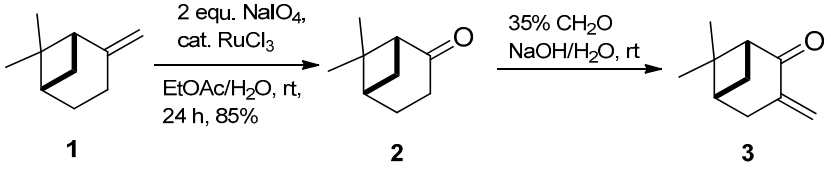
Besides their chemical interests, many compounds containing 1-amino-2,3-diol functionalities display remarkable pharmacological activities. For example, Abbott-aminodiol bears the core of the drug Zankiren® exhibiting renin-inhibitory activity [45,46]. Aminodiols have also been reported to have expressed biological properties such as a gastro-protective effect [47] or HIV protease [48] inhibition and antiviral activity [49–51].

In the present paper we report the diastereoselective synthesis of new aminodiol derivatives as potential chiral ligands in the asymmetric addition of Et_2Zn to aldehydes starting from commercially available natural (–)-*β*-pinene. These compounds, the regioisomers of pinane-based 3-amino-1,2-diols, were prepared from *α*-pinene [36]. In addition, we planned to develop a molecular model through which the interpretation of the catalytic pathway of the reaction and the catalytic activities of the chiral aminodiol derivatives should be possible.

2. Results

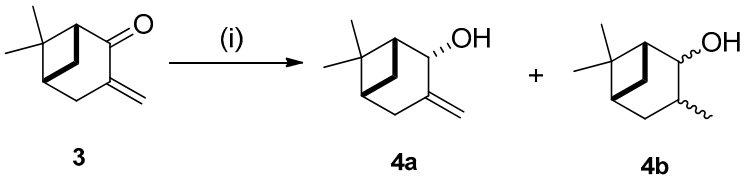
2.1. Synthesis of Allylic Alcohol 4a

Key intermediate 3-methylenenopinone **3** was prepared from commercially available (–)-*β*-pinene **1** by oxidation with the $NaIO_4/RuCl_3$ system to afford (–)-nopinone **2**. The resulting (–)-nopinone was converted into (–)-3-methylenenopinone **3** by applying formaldehyde in alkaline condition according to literature methods [52,53] (Scheme 1).



Scheme 1. Preparation of (–)-3-methylenenopinone.

Reduction of **3** with $NaBH_4$ in various solvents gave a mixture of **4a** and **4b** (Scheme 2, Table 1). It is important to note that whereas allylic alcohol **4a** was formed in a highly stereoselective manner, **4b** exists as a 4:1 mixture of two *cis*-diastereomers (*diexo* and *diendo*, based on ^{1}H-NMR measurement and comparison with data in the literature) [54,55].



Scheme 2. (i) $NaBH_4$ (2 equ.) and $CeCl_3.7H_2O$ (1 equ.), 0 °C, 0.5 h, 87%

Table 1. Stereoselective reduction of 3 according to Scheme 1.

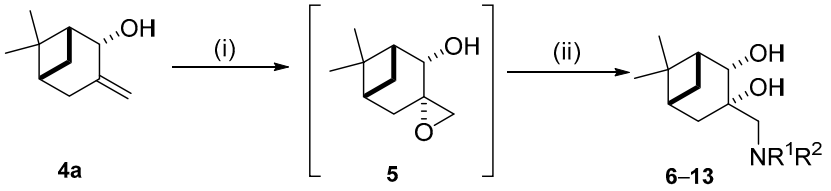
Entry	Reductant	Additive	Solvent	T (°C)	t (h)	Ratio 4a/4b [a]	Yield [b] (%)
1	$NaBH_4$	-	MeOH	−20	6	3:1	86
2	$NaBH_4$	-	MeOH	0	1	1:1	86
3	$NaBH_4$	$CeCl_3$	MeOH	0	0.5	100:0	87
5	$NaBH_4$	-	Et_2O	0	3	3:1	76
4	$NaBH_4$	-	EtOH	0	48	1:3	84

[a] Based on ^{1}H-NMR measurements of the crude product. [b] Isolated, combined yield of **4a** and **4b**.

When Et_2O was applied as solvent, **4a** was formed as the main product (**4a**:**4b** = 3:1), whereas the ratio of the two products in EtOH changed to **4a**:**4b** = 1:3. In contrast, when MeOH was used as a solvent, the two products formed in a 1:1 ratio. In addition, it is interesting to note that the ratio of **4a** and **4b** also depended on the temperature. At –20 °C in MeOH, compound **4a** was obtained as the major product (Table 1), although **4a** and **4b** could not be separated by conventional technics. Applying the condition of Luche reaction, in the presence of $CeCl_3$ as additive, **4a** was obtained as the single product. This procedure not only allowed highly regioselective reduction, but also enhanced reaction rate. The probable reason is the effect of cerium, a hard Lewis acid. Despites its weak acidity, it certainly contributes to both the regioselectivity and the high reaction rate though the coordination to the oxygen of the carbonyl function [56].

2.2. Synthesis of (–)-β-Pinene-Based Aminodiols

Epoxidation of **4a** with *t*-BuOOH in the presence of $VO(acac)_2$ as catalyst furnished epoxide **5** as a single product in a stereoselective reaction [57,58]. Since purification of epoxide **5** could not be effectively performed without its decomposition, the crude product with a purity of approximately 92% (based on ^{1}H NMR measurement) was treated with various amines to perform the aminolysis of the oxirane ring. Our previous results clearly demonstrated that when aminodiols were applied as catalysts, their *N*-substituents definitely influenced the enantioselectivity of their catalyzed reaction [22,37,59,60]. Consequently, aminodiol library **6–13** was prepared by aminolysis of **5** with secondary and primary amines in the presence of lithium perchlorate as catalyst (Scheme 3).

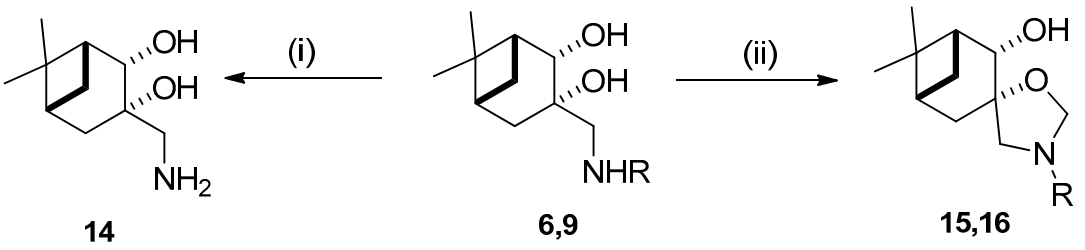


6: R^1 = H, R^2 = Bn, **7**: R^1 = H, R^2 = CH(Me)Ph (*R*), **8**: R^1 = H, R^2 = CH(Me)Ph (*S*)
9: R^1 = H, R^2 = $CH(Me)_2$, **10**: R^1 = Bn, R^2 = Bn, **11**: R^1 = Bn, R^2 = CH(Me)Ph (*R*),
12: R^1 = Bn, R^2 = CH(Me)Ph (*S*), **13**: R^1, R^2= -$(CH_2)_2$-CH(Bn)-$(CH_2)_2$-

Scheme 3. (i) $VO(acac)_2$, 70% *t*-BuOOH (2 equ.), dry toluene, 25 °C, 12 h, 76% **and** (ii) R^1R^2NH (2 equ.), $LiClO_4$ (1 equ.), MeCN, 70–80 °C, 6 h, 32%–94%**.**

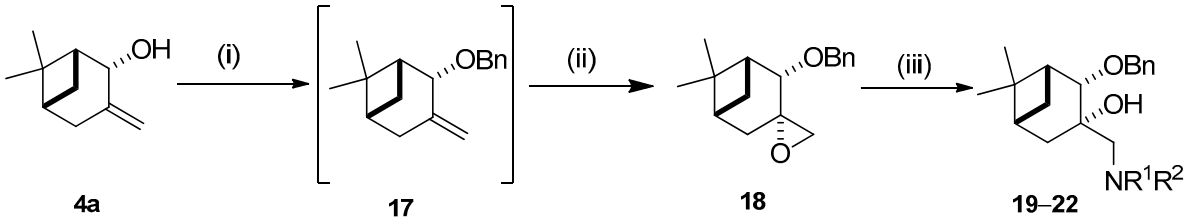
Primary aminodiol **14** was obtained in moderate yield by debenzylation of the corresponding *N*-benzyl aminodiol **6** under standard condition by hydrogenation over Pd/C (Scheme 4).

The ring closure reaction of **6** and **9** aminodiols with formaldehyde was also investigated to study the regioselectivity of the reaction [38,42,60]. When these aminodiols were reacted with formaldehyde under mild conditions, spirooxazolidine **15** and **16** were obtained in highly regioselective ring closure, with similar regioselectivity as observed in the case of pinane-based regioisomers [36]. This regioselectivity, however, is opposite to those of the carene-based analogues reported recently (Scheme 4) [37,38].



Scheme 4. (i) From 6 (R = Bn), 5% Pd/C, H_2 (1 atm), MeOH, 25 °C, 24 h, 74% and (ii) 35% HCHO, Et_2O, 25 °C, 1 h, 98% (15, R = Bn), 40% (16, R = $CH(Me)_2$).

On the other hand, to assess the importance of the secondary hydroxyl group in the catalytic application of our aminodiols, allylic alcohol **4a** was transformed into *O*-benzyl derivative **17**. The separation of **16** and benzyl bromide was unsuccessful using classical chromatography methods. Therefore, **17** was transformed with *m*CPBA to epoxide **18** and the latter could be easily purified (in contrast to its epoxyalcohol analogue **5**) on a gram scale by simple column chromatography in good yield [61–64]. The aminolysis of the formed oxirane ring of **18** with different amines afforded *O*-benzyl aminodiols **19–22** (Scheme 5) [22,59].



19: R^1 = H, R^2 = Bn, **20**: R^1 = H, R^2 = CH(Me)Ph (*R*), **21**: R^1 = H, R^2 = CH(Me)Ph (*S*)
22: R^1 = H, R^2 = $CH(Me)_2$

Scheme 5. (i) 60% NaH (1 equ.), dry THF, 25 °C, 1 h; then BnBr (1.5 equ.), KI (1 equ.), 60–70 °C, 12 h, 62%; (ii) *m*CPBA (2 equ.), Na_2HPO_4. $2H_2O$ (3 equ.), 25 °C, 2 h, 46% and (iii) RNH_2 (2 equ.), $LiClO_4$ (1 equ.), MeCN, 70–80 °C, 6 h, 30%–36%.

The relative configurations of both compounds **6–13** and **19–22** were assigned by means of NOESY experiments: reliable NOE signals were observed between the H-10 and H-2, H-6 as well as H-2 and H-6 protons (Figure 1).

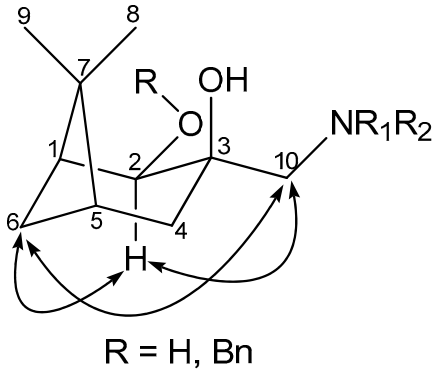
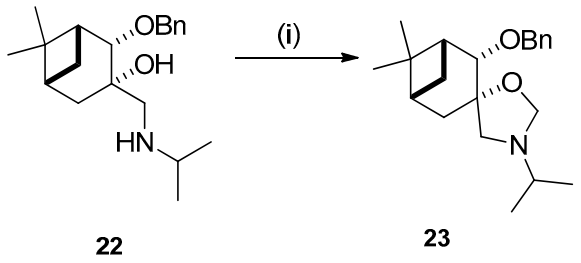


Figure 1. Determination of the structure of aminodiols by NOESY.

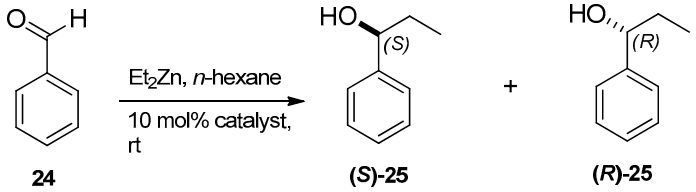
The regioselectivity of the ring closure of **22** with formaldehyde resulting in spirooxazolidine **23** (Scheme 6) was also investigated [38,42,60].



Scheme 6. (i) 35% HCHO, Et_2O, 25 °C, 1 h, 50%.

2.3. Application of Aminodiols as Chiral Ligands for Catalytic Addition of Diethylzinc to Aldehydes

Applying aminodiols **6–15** and **19–23** as chiral catalysts in the addition of diethylzinc to benzaldehyde (**24**), enantiomeric mixture of (*S*)- and (*R*)-1-phenyl-1-propanol **25** was obtained (Scheme 7).



Scheme 7. Model reaction for enantioselective catalysis.

The results are presented in Table 2. The enantiomeric excess of 1-phenyl-1-propanols (*S*)-**25** and/or (*R*)-**25** was determined by chiral GC (CHIRASIL-DEX CB column) according to literature methods [65,66]. Low to good enantioselectivities were observed. The results found clearly show that all aminodiols favored the formation of the *(R)*-enantiomer of **25**. In contrast, the application of **20** led to (*S*)-enantiomer **25** as the main product. Aminodiol **10** and **21** afforded the best *ee* value (*ee* = 80%) with an (*R*)-selectivity, whereas *O*-benzyl aminodiol **20** showed the best *ee* value (*ee* = 74%) with an (*S*)-selectivity. Moreover, enantioselectivities were also observed in the addition of diethylzinc to benzaldehyde catalyzed by aminodiols **6–8**, whereas lower, but still good selectivities were obtained with the use of *O*-benzyl aminodiol derivatives **19–22**. We suppose that the highly rigid structure of *O*-benzyl aminodiol derivatives in the transition states leads to better selectivities when compared to flexible moieties. Furthermore, our results clearly indicate that the spirooxazolidine ring (ligand **15** and **23**) has weaker catalytic performance compared with fused 1,3-oxazine systems [37,38]. These results show good accordance with those observed with sabinane- or pinane-based spirooxazolidines were reported in our earlier studies [40,60].

Table 2. Addition of diethylzinc to benzaldehyde, catalyzed by aminodiol derivatives.

Entry	Ligand [a]	Yield [b] (%)	*ee* [c] (%)	Configuration [d]
1	**6**	83	5	*(R)*
2	**7**	92	23	*(R)*
3	**8**	80	31	*(R)*
4	**9**	85	4	*(R)*
5	**10**	85	80	*(R)*
6	**11**	90	3	*(R)*
7	**12**	95	16	*(R)*
8	**13**	80	60	*(R)*
9	**14**	83	–	–
10	**15**	83	26	*(R)*
11	**16**	85	35	*(R)*

12	**19**	95	73	*(R)*
13	**20**	87	74	*(S)*
14	**21**	83	80	*(R)*
15	**22**	80	40	*(R)*
16	**23**	93	10	*(R)*

[a] 10 mol%. [b] Are given after silica column chromatography. [c] Determined by measuring the ee of the crude product by GC (Chirasil-DEX CB column). [d] Determined by comparing optical rotations and the t_R of GC analysis with the literature data [65,66].

The best (*R*)-selectivity can be explained with the steric effect of *O*-benzyl and *N*-(*S*)-1-phenylethyl substituent as it is given on Figure 2. The carbon of ethyl group of Et_2Zn can attack the carbonyl group from the less hindered *Re* face resulting in (*R*)-**25** as a main product.

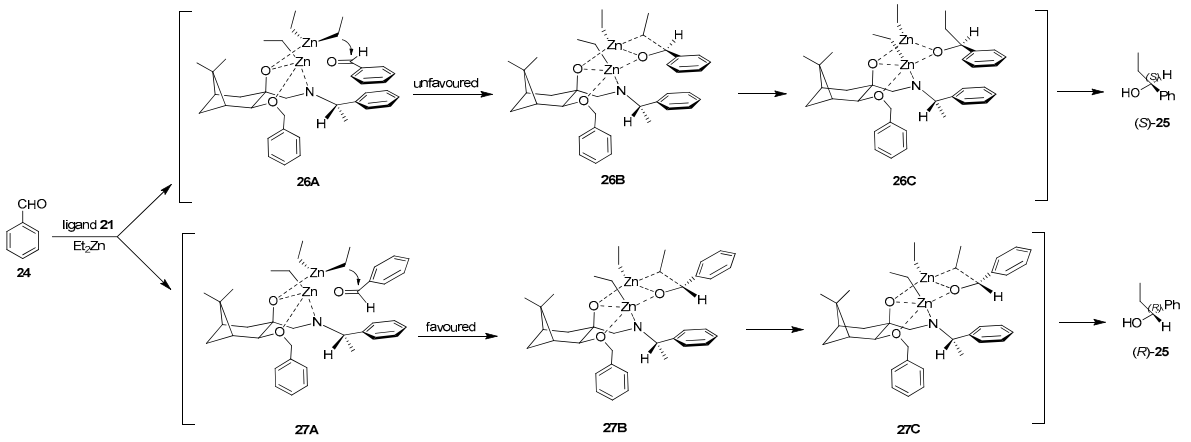
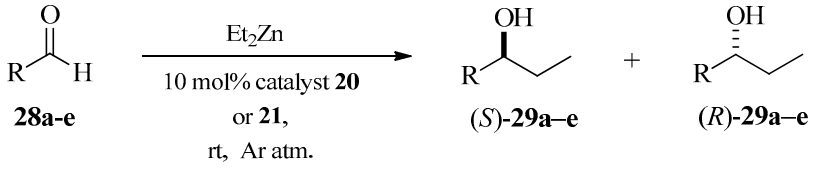


Figure 2. Proposed transition state for the asymmetric addition with **21.**

With best catalysts **20** and **21**, the diethylzinc addition reaction was extended to further aromatic and aliphatic aldehydes (Scheme 8). Our results are presented in Table 3. 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 the literature methods [37].



Scheme 8. Model reaction for enantioselective catalysis.

In order to get insight into the mechanism of chiral control over the ethyl-transfer exerted by the pinane ligand, first we carried out modeling studies at the Hartree–Fock level of theory [67] using LANL2DZ basis set [68] on **27A** comprising benzaldehyde coordinated to Zn-centers and on **27C** with covalently bonded *R*-carbinol (Figure 3). Both complexes were identified as local minima on the potential energy surface (PES). The transition state of the ethyl transfer **27B** was located by QST2 method [69] as a saddle point on the PES. In accord with the general expectations, the ethyl transfer was found to be a highly exothermic step accompanied by a significant decrease in the Gibbs free energy (–50.5 kcal/mol), but proceeds via a high activation barrier (+30.5 kcal/mol). It is of pronounced significance that the attempts to find a local minimum representing **26A**, the benzaldehyde complex preformed for the ethyl-transfer leading to *S*-adduct have failed so far, as the optimization of all the tentative initial structures led to **27A**, the complex mentioned above, that is preformed for the formation of *R*-carbinol. These findings suggest that the formation of S-carbinol can be ascribed to a

competitive process that takes place without the involvement of the pinane ligand affording racemic product, while the investigated ligand seems to promote the exclusive formation of the *R*-carbinol product.

Table 3. Addition of diethylzinc to aldehydes, catalyzed by 10 mol % 20 or 21.

Entry	Catalyst	Products	R	Yield [a] (%)	*ee* [b] (%)	Configuration [c]
1	**20**	**29a**	(4-MeO)C_6H_4	80	92	*(S)*
2	**20**	**29b**	(3-MeO)C_6H_4	78	84	*(S)*
3	**20**	**29c**	(3-Me)C_6H_4	75	78	*(S)*
4	**21**	**29a**	(4-MeO)C_6H_4	83	85	*(R)*
5	**21**	**29b**	(3-MeO)C_6H_4	92	87	*(R)*
6	**21**	**29c**	(3-Me)C_6H_4	80	84	*(R)*
7	**21**	**29d**	cyclohexyl	85	48	*(R)*
8	**21**	**29e**	*n*-butyl	80	45	*(R)*

[a] Are given after silica column chromatography. [b] Determined on the crude product by HPLC (Chiracel OD-H) or GC (Chirasil-DEX CB column). [c] Determined by comparing the t_R of the HPLC analysis and the optical rotation with the literature data [37].

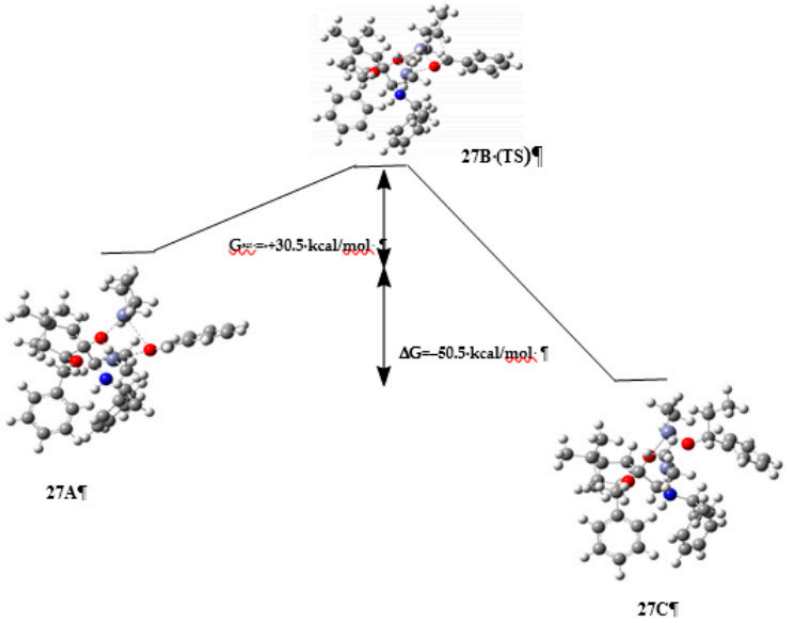


Figure 3. Reaction coordinate with activation barrier and thermodynamics of the ethyl transfer connecting complexes **27A** and **27C** via transition state **27B** optimized by the HF/LANL2DZ method.

All calculations were carried out by using Gaussian 09 software package [70]. The optimized structures are available from the authors.

3. Discussion

Starting from natural (–)-*β*-pinene, a monoterpene-based 3-amino-1,2-diol library has been created via the epoxide ring opening of epoxyalcohol as key intermediate, whereas the reactions of *N*-substituted aminodiols with formaldehyde resulted in spirooxazolidines with high regioselectivity. Moreover, *O*-benzylation of key allylic alcohol intermediate led to *O*-benzyl aminodiols by aminolysis of its epoxide. The ring closure of *O*-benzyl, *N*-isopropyl aminodiol furnished the corresponding spirooxazolidine. Aminodiol derivatives were proven reliable chiral catalysts in the enantioselective addition of diethylzinc to aldehydes. The enantioselective nature of the catalytic activity proved to be *N*- substituent-dependent, and molecular modeling was applied to

explain this phenomenon. As a result of the modeling, the *O*-benzyl and *N*-(*S*)-1-phenylethyl substituent aminodiol **21** provided high enantiomeric excess values (80% *ee* with (*R*) selectivity) in the model reactions. This ligand also proved to be excellent catalysts in the additions of diethylzinc to either aromatic or aliphatic aldehydes.

4. Materials and Methods

4.1. Materials and General Methods

^{1}H- and ^{13}C- NMR spectra were obtained on a Bruker Avance DRX 500 (Bruker Biospin, Karlsruhe, Baden Württemberg, Germany) [500 and 125 MHz, respectively, δ = 0 ppm (TMS)]. Chemical shifts (δ) are expressed in ppm and related to TMS as internal reference. J values are given in Hz. GC measurements were made on a Perkin-Elmer Autosystem KL GC consisting of a Flame Ionization Detector (Perkin-Elmer Corp., Norwalk, CT, USA) and a Turbochrom Workstation data system (Perkin-Elmer Corporation Norwalk, USA). *O*-acetyl derivatives of chiral secondary alcohol enantiomers were separated on a CHIRASIL-DEX CB column (2500 mm × 0.265 mm I.D., Agilent Technologies, Inc., Santa Clara, CA, USA). Microanalyses were achieved on a Perkin–Elmer 2400 elemental analyzer (PerkinElmer Inc., Waltham, MA, USA).

Optical rotations were determined with a Perkin–Elmer 341 polarimeter (PerkinElmer Inc., Shelton, CT, USA). Melting points were measured on a Kofler apparatus (Nagema, Dresden, Germany) and the values are uncorrected. Column chromatography of crude products was performed on Merck Kieselgel 60 (230–400 mesh ASTM, Merck Co., Darmstadt, Germany). Headaway of reactions was followed on Merck Kieselgel 60 F254-precoated TLC plates (0.25 mm thickness, Merck Co., Darmstadt, Germany).

(−)-*β*-Pinene 1 is commercially available from Merck Co (Cat. No.: 402753, Merck Co., Darmstadt, Germany) and its *ee* value was defined by Merck Co as 97%. The purity of crude products was examined by ^{1}H NMR in each case and we could not observe the presence of any other diastereoisomer in any case. All chemicals and solvents were used as supplied (Molar Chemicals Ltd., Halásztelek, Hungary; Merck Ltd., Budapest, Hungary and VWR International Ltd., Debrecen, Hungary). THF and toluene were dried over Na wire. Synthesis of (−)-nopinone 2 and (−)-3-methylenenopinone 3 were carried out as given in literature procedures, and all physical and chemical properties of 2 and 3 were similar to those described therein [50,51]. All ^{1}H-, ^{13}C- NMR, HMQC, HMBC and NOESY spectra are found in the Supporting Information.

4.2. (1R,2R,5R)-6,6-Dimethyl-3-Methylenebicyclo [3.1.1]heptan-2-ol (4a)

A suspension of $CeCl_3.7H_2O$ (2.46 g, 6.6 mmol) in MeOH (50.0 mL) was added to an ice-cooled solution of **3** (1.0 g, 6.6 mmol) in MeOH (50.0 mL). The reaction mixture was stirred in an ice bath for 30 min before $NaBH_4$ (0.5 g, 13.2 mmol) was slowly added to the mixture. Stirring was continued for 30 min at 0 °C. When the reaction was complete, the mixture was evaporated at 20 °C then poured into brine and the product was extracted with Et_2O (3 × 150 mL). The combined organic phase was washed with 3.5% HCl aqueous solution (100 mL) and dried (Na_2SO_4). After evaporation of the solvent in vacuo, the crude product **4a** was used without further purification for the next step.

Yield: 87%, white crystals. m.p.: 51–55 °C. $[\alpha]_D^{20}$=+78 (c 0.255, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84–0.87 (1H, m), 1.03 (3H, s), 1.25 (3H, s), 1.94–1.95 (1H, m), 2.09–2.12 (1H, m), 2.31–2.36 (1H, m), 2.56–2.77 (2H, m), 4.48 (1H, s), 5.16–5.42 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.7, 27.1, 29.6, 34.4, 38.1, 39.6, 46.4, 75.6, 114.2, 148.6. Anal. Calculated for $C_{10}H_{16}O$ (152.24): C 78.90, H 10.59; found: C 78.95, H 10.57.

4.3. (1R,2R,5R)-6,6-Dimethylspiro[bicyclo[3.1.1]heptane-3,2'-oxiran]-2-ol (5)

To the solution of **4a** (1.0 g, 6.6 mmol) in dry toluene (50 ml), catalytic amount of $VO(acac)_2$ (7.0 mg) was added. The mixture was stirred for 30 min then *t*-BuOOH (70% solution in water, 1.7 g, 13.2 mmol), dried briefly (Na_2SO_4), was added dropwise at 25 °C. Stirring was continued (20 h) whereupon KOH (2.0 g) in brine (80.0 ml) was added. The mixture was extracted with toluene (3 ×

100 mL), the organic layer was dried (Na_2SO_4) and evaporation at 20 °C gave compound **5** (84%) as yellow oil. Crude product **5** was used for the next step.

4.4. General Procedure for Ring Opening of Epoxide 5 with Primary and Secondary Amines

To a solution of the appropriate amine (1.2 mmol) in MeCN (5.0 mL) and $LiClO_4$ (0.06 g, 0.6 mmol), solution of epoxide **5** or **18** (0.6 mmol) in MeCN (5.0 mL) was added. After 6 h reflux the reaction was found to be completed (indicated by TLC), and the mixture was evaporated to dryness, the residue was dissolved in water (15.0 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase was dried (Na_2SO_4), filtered and concentrated. The purification of the crude product was accomplished by column chromatography on silica gel with an appropriate solvent mixture resulting in compounds **6**–**13** or **19**–**22**, respectively.

4.4.1. (1*R*,2*R*,3*S*,5*R*)-3-((Benzylamino)methyl)-6,6-Dimethylbicyclo [3.1.1]heptane-2,3-diol (6)

Purified by column chromatography on silica gel (*n*-hexane/EtOAc = 1:2). Yield: 95%, yellow crystals; m.p.: 170–175 °C. $[\alpha]_D^{20}$= +7 (c = 0.27, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.80 (1H, d, *J* = 10.8 Hz), 1.09 (3H, s), 1.20 (3H, s), 1.87–1.90 (2H, m), 2.17–2.23 (3H, m), 2.66 (2H, s), 3.81–3.84 (2H, m), 7.26–7.35 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.9, 27.0, 27.5, 37.2, 40.4, 40.6, 47.0, 52.3, 59.7, 66.1, 73.8, 129.1, 129.7, 130.2, 130.2. Anal. Calculated for $C_{17}H_{25}NO_2$ (275.39): C 74.14, H 9.15, N 5.09; found: C 74.19, H 5.13, N 5.11.

4.4.2. (1*R*,2*S*,3*S*,5*R*)-6,6-Dimethyl-3-((((*R*)-1-phenyl-ethyl)amino)methyl)bicyclo[3.1.1]heptane-2,3-diol (7)

Purified by column chromatography on silica gel (*n*-hexane/EtOAc = 1:2) to Yield: 43%, yellow crystals, m.p.: 112–116 °C. $[\alpha]_D^{20}$=+36 (c=0.26, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.76–0.80 (1H, m), 1.07 (3H, s), 1.19 (3H, s), 1.41 (3H, d, *J* = 6.5 Hz), 1.78–1.86 (2H, m), 2.11–2.22 (3H, m), 2.48 (1H, d, *J* = 11.4 Hz), 2.60 (1H, d, *J* = 11.4 Hz), 3.81–3.84 (2H, m), 7.24–7.36 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$):δ = 21.3, 23.9, 27.3, 27.8, 37.3, 41.0, 41.3, 47.3, 58.1, 62.6, 67.3, 76.5, 126.6, 127.3, 128.7. Anal. Calculated for $C_{18}H_{27}NO_2$ (289.42): C 74.70, H 9.40, N 4.84; found: C 74.73, H 9.44, N 4.80.

4.4.3. (1*R*,2*S*,3*S*,5*R*)-6,6-Dimethyl-3-((((*S*)-1-phenyl-ethyl)amino)methyl)bicyclo[3.1.1]heptane-2,3-diol (8)

Purified by column chromatography on silica gel (*n*-hexane/EtOAc = 1:2) to Yield: 45%, yellow oil. $[\alpha]_D^{20}$=-3 (c = 0.27, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.68 (1H, d, *J* = 9.1 Hz), 1.08 (3H, s), 1.18 (3H, s), 1.45 (3H, d, *J* = 6.5 Hz), 1.81–1.86 (2H, m), 2.14–2.20 (3H, m), 2.46–2.48 (1H, d, *J* = 11.9 Hz), 2.56–2.58 (1H, d, *J* = 11.9 Hz), 3.75–3.84 (2H, m), 7.24–7.35 (5H ,m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.5, 23.7, 27.3, 27.7, 37.3, 41.0, 41.5, 47.2, 58.6, 62.7, 67.3, 76.1, 126.5, 127.4, 128.7. Anal. Calculated for $C_{18}H_{27}NO_2$ (289.42): C 74.70, H 9.40, N 4.84; found: C 74.73, H 9.44, N 4.80.

4.4.4. (1*R*,2*R*,3*S*,5*R*)-3-((Disopropylamino)methyl)-6,6-Dimethylbicyclo-[3.1.1]heptane-2,3-diol (9)

Purified by column chromatography on silica gel (*n*-hexane/EtOAc = 1:2) then recrystallized in Et_2O. Yield: 32%, yellow crystals, m.p.: 190–194 °C. $[\alpha]_D^{20}$= +8 (c = 0.26, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (1H, d, *J* = 10.7 Hz), 1.04 (3H, s), 1.22 (3H, s), 1.44 (6H, d, *J* = 6.2 Hz), 1.95–1.97 (2H, m), 2.24–2.35 (3H, m), 3.00 (1H, d, *J* = 11.9 Hz), 3.12 (1H, d, *J* = 11.9 Hz), 3.49–3.55 (1H, m), 4.15 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.2, 19.4, 22.0, 27.0, 27.5, 37.3, 40.5, 42.0, 47.0, 52.7, 58.7, 66.1, 73.6. Anal. Calculated for $C_{13}H_{25}NO_2$ (227.35): C 68.68, H 11.08, N 6.16; found: C 68.70, H 11.03, N 6.12.

4.4.5. (1*R*,2*S*,3*S*,5*R*)-3-((Dibenzylamino)methyl)-6,6-Dimethylbicyclo[3.1.1]heptane-2,3-diol (10)

Purified by column chromatography on silica gel (*n*-hexane/EtOAc = 9:1). Yield: 40%, yellow oil. $[\alpha]_D^{20}$=+16 (c=0.255, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.51 (1H, d, *J* = 9.2 Hz), 1.06 (3H, s), 1.15 (3H, s), 1.57 (2H, s), 1.80–1.82 (1H, m), 1.90–1.94 (1H, m), 2.08–2.11 (3H, m), 2.63–2.66 (1H, d, *J* =

13.7 Hz), 2.72–2.75 (1H, d, *J* = 13.7 Hz), 3.05 (1H, d, *J* = 6.1 Hz), 3.49 (1H, d, *J* = 4.0 Hz), 3.74 (4H, s), 3.78–3.80 (1H, m), 4.62 (1H, s), 7.23–7.34(10H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.4, 27.3, 27.8, 37.2, 41.2, 43.1, 47.2, 59.6, 67.9, 68.9, 77.4, 127.3, 128.4, 129.2, 139.0. Anal. Calculated for $C_{24}H_{31}NO_2$ (365.52): C 78.86, H 8.55, N 3.83; found: C 78.83, H 8.50, N 3.79.

4.4.6. (1*R*,2*S*,3*S*,5*R*)-3-((Benzyl((*R*)-1-phenylethyl)amino)methyl)-6,6-dimethylbicyclo[3.1.1] heptane-2,3- diol (11)

Purified by chromatography on silica gel column (*n*-hexane/EtOAc = 9:1). Yield: 30%, white crystals, m.p.: 120–125 °C. $[\alpha]_D^{20}$= +45 (c = 0.28, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.49 (1H, d, *J* = 10.1 Hz), 1.05 (3H, s), 1.14 (3H, s), 1.41–1.42 (3H, d, *J* = 6.8 Hz), 1.57 (1H, s), 1.82–1.83 (1H, m), 1.98–2.03 (2H, m), 2.08–2.12 (1H, m), 2.15-2.18 (1H, m), 2.48–2.50 (1H, d, *J* = 13.7 Hz), 2.80–2.83 (1H, d, *J* = 13.7 Hz), 2.95 (1H, d, *J* = 5.7 Hz), 3.55–3.57 (1H, m), 3.77 (2H, s), 4.08–4.12 (1H, m), 4.85 (1H, s), 7.25–7.36 (10 H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.4, 21.3, 27.3, 28.0, 37.1, 41.3, 43.8, 47.1, 56.0, 57.6, 64.4, 67.3, 77.5, 127.2, 128.2, 128.2, 128.5, 128.9, 139.7, 141.9. Anal. Calculated for $C_{25}H_{33}NO_2$ (379.54): C 79.11, H 8.76, N 3.69; found: C 79.08, H 8.81, N 3.65.

4.4.7. (1*R*,2*S*,3*S*,5*R*)-3-((Benzyl((*S*)-1-phenylethyl)amino)methyl)-6,6-dimethylbicyclo[3.1.1] heptane-2,3- diol (12)

Purified by column chromatography on silica gel (*n*-hexane/EtOAc = 9:1). Yield: 60%, yellow oil. $[\alpha]_D^{20}$=-28 (c=0.26, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.62–0.65 (1H, m), 1.05 (3H, s), 1.15 (3H, s), 1.42 (3H, d, *J* = 6.3 Hz), 1.76–1.79 (1H, m), 1.81–1.85 (1H, m), 1.99–2.03 (1H, m), 1.15–2.18 (2H, m), 2.58 (1H, d, *J* = 14.2 Hz), 2.79 (1H, d, *J* = 13.8 Hz), 3.66–3.68 (1H, d, *J* = 12.8 Hz), 3.82–3.85 (1H, d, *J* = 13.6 Hz), 3.86 (1H, s), 5.29 (1H, s), 7.24-7.35 (10H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.7, 21.3, 27.3, 28.2, 37.0, 41.1, 43.8, 47.2, 55.4, 57.3, 65.0, 66.8, 78.3, 127.2, 127.3, 128.2, 128.2, 128.5, 128.9, 139.41, 142.0. Anal. Calculated for $C_{25}H_{33}NO_2$ (379.54): C 79.11, H 8.76, N 3.69; found: C 79.08, H 8.81, N 3.65.

4.4.8. (1*R*,2*S*,3*S*,5*R*)-3-((4-Benzylpiperidin-1-yl)methyl)-6,6-dimethylbicyclo[3.1.1]heptane-2,3-diol (13)

Purified by column chromatography on silica gel (*n*-hexane/EtOAc = 1:1). Yield: 55%, yellow oil. $[\alpha]_D^{20}$= +14 (c = 0.26, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.75 (1H, d, *J* = 9.6 Hz), 1.10 (3H, s), 1.19 (3H, s), 1.25–1.33 (2H, m), 1.51–1.63 (4H, m), 1.85–1.89 (1H, m), 1.91–1.95 (1H, m), 2.17–2.28 (5H, m), 2.48–2.56 (4H, m), 2.89–3.01 (2H, m), 3.68–3.76 (2H, m), 7.12–7.28 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.2, 27.5, 28.4, 32.4, 41.2, 43.1, 44.6, 47.1, 54.3, 55.5, 74.4, 152.8, 128.2, 129.1, 131.7. Anal. Calculated for $C_{22}H_{33}NO_2$ (343.51): C 76.92, H 9.68, N 4.08; found: C 76.88, H 9.71, N 4.13.

4.4.9. (1*R*,2*S*,3*S*,5*R*)-3-((Benzylamino)methyl)-2-(benzyloxy)-6,6-dimethylbicyclo[3.1.1]heptan-3-ol (19)

Purified by column chromatography on silica gel (*n*-hexane/EtOAc = 1:2). Yield: 32%, yellow oil. $[\alpha]_D^{20}$=+35 (c=0.27, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.95 (3H, s), 1.23 (3H, s), 1.79 (2H, d, *J* = 10.1 Hz), 1.90–1.92 (3H, m), 2.16–2.24 (2H, m), 2.42–2.45 (1H, m), 3.31 (1H, d, *J* = 11.8 Hz), 3.69 (1H, d, *J* = 13.1 Hz), 3.77 (1H, d, *J* = 13.5 Hz), 3.87 (1H, d, *J* = 4.6 Hz), 4.21 (1H, d, *J* = 10.5 Hz), 4.59 (1H, d, *J* = 11.4 Hz), 7.10–7.12 (2H, m), 7.20–7.32 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.2, 24.7, 27.3, 37.5, 38.9, 40.0, 41.2, 54.2, 56.7, 70.0, 71.4, 89.2, 126.9, 127.4, 127.4, 127.9, 128.4, 128.4, 138.8. Anal. Calculated for $C_{24}H_{31}NO_2$ (365.52): C 78.86, H 8.55, N 3.83; found: C 78.90, H 8.51, N 3.80.

4.4.10. (1*R*,2*S*,3*S*,5*R*)-2-(Benzyloxy)-6,6-dimethyl-3-((((*R*)-1-phenylethyl)amino)methyl)bicyclo[3.1.1] heptan-3-ol (20)

Purified by column chromatography on silica gel (*n*-hexane/EtOAc = 1:2). Yield: 36%, white crystals, m.p. : 84–86 °C. $[\alpha]_D^{20}$= +4 (c = 0.26, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (3H, s), 1.22 (3H, s), 1.24 (3H, d, *J* = 6.1 Hz), 1.79 (1H, d, *J* = 10.0 Hz), 1.84–1.90 (3H, m), 2.01 (1H, d, *J* = 10.6 Hz), 2.17–2.22 (1H, m), 2.43–2.46 (1H, dd, *J* = 4.6 Hz, 11.6 Hz), 3.03 (1H, d, *J* = 11.5 Hz), 3.61 (1H, dd, *J* = 6.7

Hz, 13.5 Hz), 3.89 (1H, d, *J* = 4.3 Hz), 4.19 (1H, d, *J* = 11.6 Hz), 4.60 (1H, d, *J* = 10.3 Hz), 6.88–6.90 (2H, m), 7.16–7.19 (3H, m), 7.25–7.37 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.2, 24.5, 34.8, 27.3, 37.5, 38.8, 40.0, 47.2, 41.1, 55.3, 58.9, 70.2, 71.3, 89.5, 126.0, 126.6, 127.6, 127.9, 128.4, 128.5. Anal. Calculated for $C_{25}H_{33}NO_2$ (379.25): C 79.11, H 8.76, N 3.69; found: C 79.10, H 8.80, N 3.73.

4.4.11. (1*R*,2*S*,3*S*,5*R*)-2-(Benzyloxy)-6,6-dimethyl-3-((((*S*)-1-phenylethyl)amino)methyl)bicyclo[3.1.1] heptan-3-ol (21)

Purified by column chromatography on silica gel (*n*-hexane/EtOAc = 1:2). Yield: 30%, yellow oil. $[\alpha]_D^{20}$ = −10 (c = 0.28, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.95 (3H, s), 1.20 (3H, d, *J* = 7.0 Hz), 1.22 (3H, s), 1.75 (1H, d, *J* = 10.1 Hz), 1.81–1.83 (2H, m), 1.86–1.88 (1H, m), 2.10 (1H, d, *J* = 11.2 Hz), 2.16–2.20 (1H, m), 2.44 (1H, q, *J* = 4.9 Hz, 11.0 Hz), 3.21 (1H, d, *J* = 11.0 Hz), 3.70 (1H, dd, *J* = 6.3 Hz, 13.4 Hz), 3.90 (1H, d, *J* = 4.2 Hz), 4.26 (1H, d, *J* = 11.5 Hz), 4.63 (1H, d, *J* = 11.5 Hz), 7.19-7.38 (10H, m). 13C NMR (125 MHz, CDCl3): δ = 22.2, 24.2, 24.7, 27.3, 37.5, 38.9, 40.0, 41.3, 54.7, 57.9, 70.1, 71.3, 89.5, 126.7, 126.9, 127.4, 127.5, 128.4, 128.4. Anal. Calculated for $C_{25}H_{33}NO_2$ (379.54): C 79.11, H 8.76, N 3.69; found: C 79.08, H 8.71, N 3.74.

4.4.12. (1*R*,2*S*,3*S*,5*R*)-2-(Benzyloxy)-3-((isopropylamino)methyl)-6,6-dimethylbicyclo[3.1.1]heptan-3-ol (22)

Purified by column chromatography on silica gel (*n*-hexane/EtOAc = 1:9) then recrystallized from Et_2O. Yield: 36%, yellow crystals, m.p.: 176–179 °C. $[\alpha]_D^{20}$ = +33 (c = 0.26, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 (3H, d, *J* = 6.1 Hz), 1.04 (3H, s), 1.16 (3H, d, *J* = 7.0 Hz), 1.30 (3H, s), 1.74 (1H, d, *J* = 10.3 Hz), 2.01–2.03 (1H, m), 2.07–2.16 (2H, m), 2.25–2.30 (1H, m), 2.62 (1H, dd, *J* = 4.9 Hz, 6.0 Hz), 3.13–3.23 (2H, m), 3.30–3.34 (1H, m), 4.28 (1H, d, *J* = 4.2 Hz), 4.41 (1H, d, *J* = 8.8 Hz), 4.56 (1H, d, *J* = 9.3 Hz), 6.40 (1H, s), 6.83 (1H, s), 7.29–7.43 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.4, 19.4, 22.2, 24.4, 27.0, 37.1, 39.6, 39.8, 40.7, 51.9, 52.7, 69.8, 71.1, 85.8, 128.4, 128.7, 129.2, 137.4. Anal. Calculated for $C_{20}H_{31}NO_2$ (317.24): C 75.67, H 9.84, N 4.41; found: C 75.70, H 9.81, N 4.46.

4.5. (1R,2R,3S,5R)-3-(Aminomethyl)-6,6-dimethylbicyclo-[3.1.1]heptane-2,3-diol (14)

To a suspension of 5% Pd/C (87 mg) in *n*-hexane/EtOAc = 1:1 (20 mL) was added aminodiol **6** (0.29 g, 1.0 mmol) in *n*-hexane/EtOAc = 1:1 (20 mL). The mixture was stirred under a hydrogen atmosphere at 25 °C. The reaction was monitored by means of TLC and was completed after 24 h stirring at room temperature. The resulting mixture was filtered through a Celite pad and the solution was evaporated to dryness. The obtained crude product was recrystallized in Et_2O, resulting in primary aminodiol **14** as the single product.

Yield: 74%, yellow crystals, m.p.: 204–207 °C. $[\alpha]_D^{20}$ = +10 (c = 0.27, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.90 (1H, d, *J* = 10.5 Hz), 1.03 (3H, s), 1.17 (3H, s), 1.93–2.03 (2H, m), 2.08–2.09 (1H, m), 2.19–2.24 (1H, m), 2.72 (1H, d, *J* = 12.6 Hz), 2.83 (1H, d, *J* = 12.5 Hz), 3.74 (1H, s), 4.78 (1H, s), 5.69 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 22.4, 27.6, 27.7, 37.3, 41.0, 47.1, 53.4, 66.2, 73.8. Anal. Calculated for $C_{10}H_{19}NO_2$ (185.27): C 64.83, H 10.34, N 7.56; found: C 64.80, H 10.31, N 7.61.

4.6. General Procedure for Ring Closure of Aminodiol Derivatives with Formaldehyde

To the solution of aminodiols **6**, **9** or **22** (1.8 mmol) in Et_2O (5 mL), 35% aqueous formaldehyde (20 mL) was added in one portion. The mixture was stirred at room temperature for 1 h, than made alkaline with 10% aqueous KOH (20 mL) and extracted with Et_2O (3 × 50 mL). After drying (Na_2SO_4) and solvent evaporation, crude products **15**, **16** or **23** were purified by column chromatography with an appropriate solvent mixture.

4.6.1. (1*R*,2*S*,3*S*,5*R*)-3'-Benzyl-6,6-dimethylspiro [bicyclo[3.1.1]heptane-3,5'-oxazolidin]-2-ol (15)

Purified by column chromatography on silica gel (*n*-hexane/EtOAc = 2:1). Yield: 98%, yellow oil. $[\alpha]_D^{20}$ = +8 (c = 0.25, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.80 (1H, d, *J* = 10.3 Hz), 1.01 (3H, s), 1.14 (3H, s), 1.78–1.82 (1H, m), 2.01–2.04 (1H, m), 2.12–2.23 (3H, m), 2.83 (1H, d, *J* = 10.4 Hz), 2.92 (1H,

d, *J* = 9.8 Hz), 3.74 (2H, s), 3.82 (1H, t, *J* = 3.6 Hz), 3.89 (1H, d, *J* = 3.6 Hz), 4.25 (1H, d *J* = 3.4 Hz), 4.32 (1H, d, *J* = 3.4 Hz), 7.23–7.35 (5H, m). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 22.3, 27.1, 27.5, 37.1, 40.2, 42.5, 46.3, 56.5, 71.9, 78.0, 79.2, 86.3, 127.4, 128.8, 139.4. Anal. Calculated for $C_{18}H_{25}NO_2$ (287.19): C 75.22, H 8.77, N 4.87; found: C 75.21, H 8.80, N 4.82.

4.6.2. (1*R*,5*R*)-3'-Isopropyl-6,6-dimethylspiro[bicyclo[3.1.1]heptane-3,5'-oxazolidin]-2-ol (16)

Purified by column chromatography on silica gel (*n*-hexane/EtOAc = 1:9). Yield: 40%, yellow oil. $[\alpha]_D^{20}$=+6 (c=0.255, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.89-0.91. (1H, d, *J* = 10.4 Hz), 0.98 (3H, s), 1.01-1.04 (6H, dd, J = 6.14 Hz), 1.15 (3H, s), 1.24 (1H, s), 1.78–1.81 (1H, m), 2.00–2.03 (1H, m), 2.09–2.19 (3H, m), 2.47 (1H, s), 2.64-2.68 (1H, m), 2.85-2.86 (1H, m), 1.32-1.37 (1H, m), 4.20 (1H, s), 4.34 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 22.2, 22.3, 26.9, 27.5, 37.3, 41.6, 46.3, 51.9, 69.4, 78.6, 78.9, 85.2. Anal. Calculated for $C_{14}H_{25}NO_2$ (239,36): C 70.25, H 10.53, N 5.85; found: C 70.28, H 10.50, N 5.89.

4.6.3. (1*R*,2*S*,3*S*,5*R*)-2-(Benzyloxy)-3'-isopropyl-6,6-dimethylspiro[bicyclo[3.1.1]heptane-3,5'-oxazolidine] (23)

Purified by column chromatography on silica gel (*n*-hexane/EtOAc = 4:1). Yield: 50%, yellow oil. $[\alpha]_D^{20}$= +32 (c = 0.23, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.94 (3H, s), 1.05 (6 H, d, *J* = 7.0 Hz), 1.22 (3H, s), 1.54 (1H, d, *J* = 10.0 Hz), 1.87–1.91 (1H, m), 2.16–2.23 (3H, m), 2.29–2.32 (1H, m), 2.43–2.48 (2H, m), 3.78–3.81 (2H, m), 4.24 (1H, d, *J* = 3.4 Hz), 4.46 (1H, d, *J* = 4.0 Hz), 4.58 (1H, d, *J* = 11.9 Hz), 4.62 (1H, d, *J* = 11.7 Hz), 7.23–7.35 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.0, 22.2, 22.5, 25.2, 27.1, 37.5, 39.9, 40.6, 42.7, 52.2, 58.6, 71.6, 82.5, 84.0, 87.8, 127.1, 127.2, 128.1, 139.3. Anal. Calculated for $C_{21}H_{31}NO_2$ (329.48): C 76.55, H 9.48, N 4.25; found: C 76.51, H 9.50, N 4.27.

4.7. (1R,2S,5R)-2-(Benzyloxy)-6,6-dimethyl-3-methylenebicyclo[3.1.1]heptane (17)

A suspension of NaH (60% purity, 0.26 g, 6.6 mmol) in dry THF (10.0 mL) was added to a solution of **3** (1.0 g, 6.6 mmol) in dry THF (20.0 mL). The reaction mixture was stirred at 25 °C for 30 min than KI (1.1 g, 6.6 mmol) and benzyl bromide (1.2 mL, 13.2 mmol) were added to the suspension. After stirring for 6 h at 60 °C the reaction was completed (monitored by means of TLC) and the mixture was poured into saturated NH_4Cl solution (30 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phase was dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo and the crude product **17** was used for the next step.

4.8. (1R,2S,3S,5R)-2-(Benzyloxy)-6,6-dimethylspiro[bicyclo[3.1.1]heptane-3,2′-oxirane] (18)

To a mixture of solution of **17** (0.4 g, 1.65 mmol) in CH_2Cl_2 (20 mL) and $Na_2HPO_4{\cdot}2H_2O$ (0.88 g, 4.95 mmol) in water (20 mL), *m*-chloroperbenzoic acid (70% purity, 0.81 g, 3.3 mmol) was added at 0 °C. The reaction was completed after 2 h stirring at 25 °C (indicated by means of TLC), than the mixture was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was washed with a 5% KOH solution (3 × 20 mL), then dried (Na_2SO_4) and evaporated in vacuo. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 19:1) to provide **20** as the single product.

Yield: 47%, colorless oil. $[\alpha]_D^{20}$= +48 (c = 0.26, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.10 (3H, s), 1.19–1.22 (1H, m), 1.24–1.26 (1H, m), 1.27 (3H, s), 1.34–1.35 (1H, m), 1.90 (1H, dd, *J* =3.6 Hz, *J* = 10.9 Hz), 2.01–2.04 (1H, m), 2.36–2.42 (3H, m), 2.69 (1H, d, *J* =6.0 Hz), 3.32 (1H, d, *J* = 5.4 Hz), 3.75 (1H, d, *J* = 2.5 Hz), 4.34 (1H, d, *J* = 12.3 Hz), 4.56 (1H, d, *J* = 11.4 Hz), 7.25–7.34 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.5, 26.8, 28.4, 36.0, 37.3, 40.8, 42.9, 53.3, 58.4, 71.0, 85.0, 127.3, 127.4, 128.3, 138.8. Anal. Calculated for $C_{17}H_{22}O_2$ (258.36): C 79.03, H 8.58; found: C 79.07, H 8.61.

4.9. General Procedure for the Reaction of Diethylzinc with Aldehydes in the Presence of Chiral Catalysts

The mixture of appropriate catalyst (0.15 mmol) and 1 M Et_2Zn in *n*-hexane solution (1.5 mL, 1.5 mmol) was stirred for 25 min in argon atmosphere at room temperature and then appropriate aldehyde (1.5 mmol) was added to the mixture in one portion. After 20 h of stirring at room

temperature, the reaction was quenched with saturated NH_4Cl solution (15 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layer was washed with H_2O (10 mL) and dried (Na_2SO_4) and the solvent was evaporated under vacuum resulting in **25** and **29a–e**. The *ee* and absolute configuration of the resulting phenyl-1-propanol (**25**) were determined by chiral GC on a Chirasil-DEX CB column after *O*-acetylation in Ac_2O/DMPA/pyridine [65,66] and without derivatization for 1-cyclohexyl-1-propanol (**29d**) and 3-heptanol (**29e**) [37]. Identification of **29a–c** was done by chiral HPLC analysis on a Chiralcel OD-H column with *V*(*n*-hexane)/*V*(2-propanol) = 98:2 mixture, 1.0 mL/min, 210 nm and the direction of the optical rotation of products was also checked [37].

Supplementary Materials: The following are available online at www.mdpi.com/2073-4344/10/5/474/s1, ^{1}H-, ^{13}C- NMR, HMQC, HMBC and NOESY spectra of new compounds as Figure S3–S83.

Author Contributions: Z.S. conceived and designed the experiments; M.R. performed the experiments, analyzed the data; all authors (M.R., T.M.L., F.F. and Z.S.) discussed the results and contributed to write the paper. All authors have read and agreed to the published version of the manuscript

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