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Bicyclic diols and related derivatives as catalysts for the asymmetric diethylzinc addition to benzaldehyde

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ABSTRACT

Chiral bicyclic diols based on bicyclo[2.2.2]octane and bicyclo[2.2.1]heptane have been synthesized and their catalytic capacity in the asymmetric diethylzinc addition to benzaldehyde compared with those described for previously synthesized 2,6-bicyclo[2.2.2]octane-diols (BODOLs). The influence of the number of coordinating sites and the distance between them were studied.

1. Introduction

The asymmetric addition of diethylzinc to benzaldehyde has been extensively studied,[1–3] and is a convenient test reaction for new metal coordinating ligands and catalysts. While a large number of amino alcohols have been found to be excellent catalysts for the reaction,[4] diols are often poor catalysts by themselves and are frequently used as complexes with Ti(IV). A few cases of diol catalysis in this reaction have been reported, including 2,6-bicyclo[2.2.2]octane-diols (BODOLs), presented by our group.[5–7] The yields and enantioselectivities were highly dependent on the aryl side-group at the 2-position of the BODOLs. The best catalyst was *o*-anisyl-bicyclo[2.2.2]octane-diol, giving (*R*)-1-phenylpropanol of 92% ee. In an attempt to find more efficient and selective diol-catalysts, we have synthesized novel bicyclic diols in the form of 2,6-BODOLs, 2,5-BODOLs and 2,5-bicyclo[2.2.1]heptane-diols (2,5-BHEDOLs[†]), which are presented in this report together with their ability to act as enantioselective catalysts in the diethylzinc addition to benzaldehyde.

2. Results and discussion

2.1. Synthesis of bicyclo[2.2.1]heptane- and bicyclo[2.2.2]-octane-diols

Hydroxy ketone (−)-**5** seemed to be a suitable intermediate derivative, which by some simple redox and addition reactions would lead to the type of compounds that we required. Compound (±)-**5** was previously reported by Toivonen starting from (±)-**4**,[8] which in its enantiomerically pure form in turn was described by Weissfloch and Azerad.[9] Thus, we used a modified combination of the published methods in order to synthesize (−)-**5** (Schemes 1 and 2). A suitable starting material was the commercial mixture of *endo*- and *exo*-5-norbornene-2-yl-acetate **1** (Scheme 1). Epoxidation with magnesium monoperoxyphthalate (MMPP) in aqueous ethanol, followed by recrystallization from ether afforded the pure *endo*-epoxyacetate **2**. Alkaline hydrolysis gave epoxyalcohol **3**, which was resolved by enzymatic transesterification using Novozym 435 (immobilized lipase B from *Candida antarctica)* and isopropenylacetate in toluene. In this process, the (+)-enantiomer of **3** was enantioselectively acylated by the enzyme leaving alcohol (−)-**3** in high ee. Chiral GC analysis[‡] was used to monitor the reaction, which was disrupted when the ee of alcohol (−)-**3** reached >95% (at approximately 60% conversion). The addition of 4 Å MS shortened the reaction time considerably. Ester (+)-**2** with lower ee (50–70% ee, depending on the degree of conversion) was hydrolyzed and the resulting epoxy alcohol, (+)-**3** (50–70% ee), was exposed to another ester resolution procedure. Initially, the ee of (+)-**2** was >99%, but as the reaction proceeded, the ee of (+)-**2** decreased. Therefore, the reaction was disrupted when the ee of (+)-**2** dropped below 95%, giving (+)-**2** in high ee and reasonable yield. Lipase from *Candida rugosa* has previously been used for the resolution[9] but Novozym 435 is preferred since it is more durable and could be re-used several times without any change in reactivity, if stored in toluene.

Reduction of epoxyalcohol (−)-**3** with $LiAlH_4$ gave diol (−)-**4** as the major product.[9] Diol (−)-**4** was selectively oxidized at the *endo*-hydroxyl with nitric acid giving hydroxy ketone (−)-**5**.[8] Diketone (−)-**6** was isolated as a by-product in 8% yield. The aryl side-groups

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† We suggest that the diols based upon the bicyclo[2.2.1]heptane framework should be named BHEDOLs (bicyclo[2.2.1]heptane-diols).

‡ GC analysis was performed on a Supelco beta DEX™ 120 column. The alcohol was best analyzed at 140 °C (isothermic) (t_R (−)-**3** 23.0 min, (+)-**3** 24.0 min) and the ester at 130 °C (isothermic) (t_R (+)-**2** 25.3 min, (−)-**2** 25.8 min). The conversion was calculated from the peak-areas without calibration.

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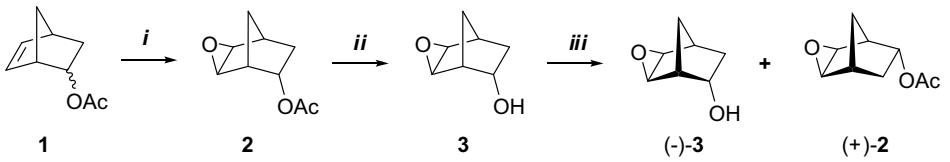
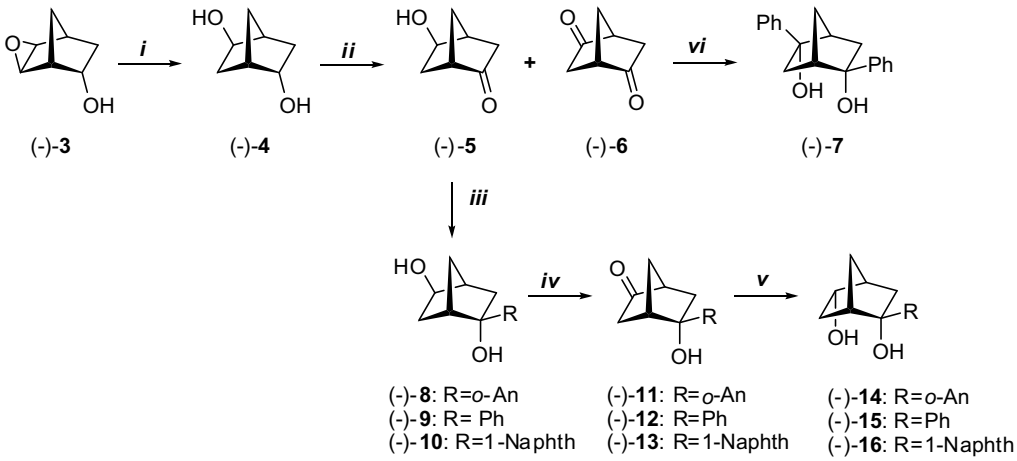


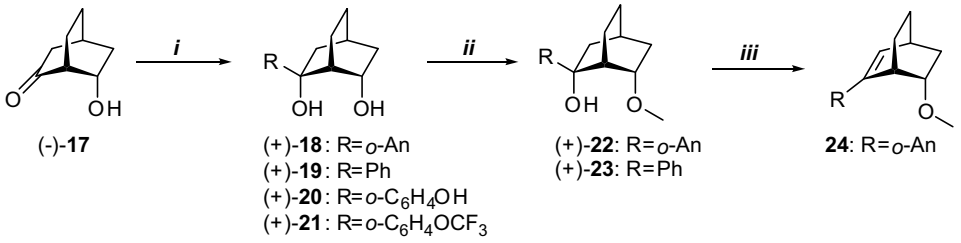
Scheme 1. Reagents and conditions: (i) (1) MMPP, EtOH/H_2O, rt, 4 h; (2) recrystallization from Et_2O; (ii) 2 M NaOH, EtOH, rt, 30 min; (iii) Novozym 435, isopropenylacetate, toluene, 4 Å MS.



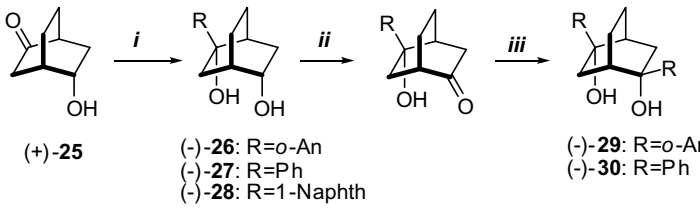
Scheme 2. Reagents and conditions: (i) $LiAlH_4$, THF, 4 h, reflux; (ii) 33% HNO_3, rt, 30 min; (iii) RMgX/RLi,, rt; (iv) TPAP, NMO, CH_2Cl_2, MS 4 Å, rt, 1.5 h; (v) $NaBH_4$, MeOH, 0 °C, 15 min; (vi) PhMgCl, THF/Et_2O, rt.

were then introduced by the reaction of hydroxy ketone (−)-**5** with the corresponding Grignard or organolithium reagent without protection of the alcohol. The C_2-symmetric diol (−)-**7** was synthesized from diketone (−)-**6** and phenylmagnesium chloride according to a literature procedure.[10] The product from the *endo*-addition was not observed in any of the reactions and the conversions were close to total in all reactions, which means that there was no problem with enolate formation. For the introduction of the phenyl and the 1-naphthyl-group, the corresponding Grignard reagents gave the cleanest reactions except for the introduction of the *o*-anisyl group, when the organolithium reagent was the better choice. Oxidation of the remaining alcohol using TPAP/NMO followed by selective reduction with $NaBH_4$ in methanol afforded diols (−)-**14**, (−)-**15** and (−)-**16**.

Diols (+)-**18** and (+)-**19** were synthesized according to procedures previously developed in our group.[11] The 2,6-BODOLs (+)-**20** and (+)-**21** were synthesized by the addition of the in situ formed organolithium reagents (from the corresponding bromoaromatic compound and butyllithium) to hydroxy ketone (−)-**17**. Mono methylated compounds (+)-**22** and (+)-**23** were obtained



Scheme 3. Reagents and conditions: (i) RMgX/RLi; (ii) MeI, KOH, THF, rt, overnight; (iii) spontaneous elimination upon storage.



Scheme 4. Synthesis of 2,5-BODOLs.[11]

from the corresponding diols by reaction with MeI and KOH in THF. Compound (+)-**22** slowly eliminated water upon standing at rt, giving unsaturated ether **24** (Scheme 3). However, it appeared more stable in benzene solution in which no elimination was observed after several weeks. To be sure of its purity, (+)-**22** was purified by chromatography and checked by ^{1}H NMR before it was used in the catalytic experiments.

Diols (−)-**26**-(−)-**30** were synthesized according to procedures previously developed by our group (Scheme 4).[11]

2.2. Catalysis

1,3-Diols lacking the rigidity of the bicyclic backbone were less efficient catalysts according to our earlier studies.[5] The bicyclic framework of the 2,6-BODOLs places the coordinating groups at a fixed distance from each other, which seemed to be important for the formation of complexes with diethylzinc. With the 2,5-BODOLs and 2,5-BHEDOLs, we have created catalysts with two other distances between the hydroxyl groups. We undertook a molecular mechanics computational energy minimization using MACROMODEL v.6.5[12] to determine the O–O distances for the three catalysts (−)-**14**, (+)-**18** and (−)-**26**. For *o*-anisyl-2,6-BODOL (+)-**18**, the distance between the two hydroxyl groups was 2.74 Å, while for *o*-anisyl-2,5-BODOL (−)-**26** the distance was 3.90 Å and for *o*-anisyl-2,5-BHEDOL (−)-**14** the distance was 3.65 Å.

The catalytic experiments were conducted in Et_2O and hexane (2:3) at 0 °C for 40 h using a catalyst loading of 5 mol %. The results from the experiments are presented in Table 1. After the reaction, the only compounds detected, besides the catalysts, were 1-phenylpropanol, benzylalcohol and recovered benzaldehyde. The low yield of 1-phenylpropanol corresponded to the high yield of the recovered benzaldehyde. Thus, the given yields also gave a good approximation of the degree of conversion. Comparing the results from 2,6-BODOL (+)-**18** and 2,5-BODOL (−)-**26**; the ee decreased from 90% to 82% and the yield from 83% to 66% as the distance between the hydroxyls increased (Table 1, entries 1 and 5). 2,5-BHEDOL (−)-**14**, on the other hand, gave only 60% ee and 52% yield even when the distance between the hydroxyl groups was close to that of the 2,5-BODOL (Table 1, entry 8). The bicyclo[2.2.1]heptane framework is more rigid than that of the bicyclo[2.2.2]octanes, which may affect the possibility to form the competent complexes.

The necessity of an extra coordinating group for 2,6-BODOLs, as indicated from previous studies,[5] was also valid for the 2,5-BODOLs and 2,5-BHEDOLs. Thus the presence of the *o*-anisyl substituent gave superior results within all three classes, compared to the phenyl and 1-naphthyl substituents. Phenyl substituted 2,5-BODOL (−)-**27** gave only 18% ee and 31% yield (entry 6) while phenyl substituted BHEDOL (−)-**15** yielded 28% of almost racemic product (2% ee, entry 9). However, 1-naphthtyl substituted BHEDOL (−)-**16** gave a moderate ee of 38%, although the yield was only 28% (entry 10).

Thus, all three O-coordinating sites seemed necessary to provide the required low-energy pathway. However, there is a possibility that the complexes only involved one of the hydroxyls and the oxygen of the side chain. To investigate this, we intended to remove the secondary hydroxyl group from (+)-**18** to obtain monoalcohol **31** (Fig. 1). We tried diverse methods for deoxygenation; conversion of the secondary alcohol to a better leaving group[13,14] with subsequent reduction,[15,16] elimination using Burgess' reagent[17] or conversion of the corresponding ketone to the thioacetal[18] or tosylhydrazone[19] followed by reduction. Disappointingly, the expected monoalcohol could not be detected in any of these attempts. However, semi-preparative chiral HPLC (OD-H column) separation of racemic 2-phenyl-bicyclo[2.2.1]heptan-2-ol, **32**, synthesized by the addition of AnMgBr to norcamphor, gave access to monoalcohol (−)-**32** in >99% ee. It was tested as a catalyst but it was inferior compared to its diol-analogue (entry 16), which indicated that all three coordinating sites indeed were necessary to reach high enantioselectivity.

Compound (+)-**22** has three coordinating sites but only one of them is a hydroxyl group, the other two being methoxy groups. It gave the best yield in this study (97%), but the enantioselectivity was much lower than for diol (+)-**18**, 26–44% ee and 90% ee, respectively (entries 14 and 1). The corresponding compound with the phenyl side chain, (+)-**23**, gave better enantioselectivity than its corresponding diol but lower yield (entries 15 and 2). Unsaturated ether **24**, the product from spontaneous elimination of water from (+)-**22**, was isolated and tested as a catalyst. As expected it gave the racemic product in low yield (25%) (entry 17). It should be noted that (+)-**22** and (+)-**23** were stable under the reaction conditions and none of the corresponding unsaturated ethers were detected after the reaction.

Both compounds (+)-**20** and (+)-**21** have three coordinating groups. Compound (+)-**20** gave a product of 72% ee in 69% yield (entry 3). The isolated enantiomer had an (*S*)-configuration, which indicated that the complex formed was different from the complex formed by (+)-**18**, which gave the (*R*)-enantiomer. This was not unexpected since the phenolic OH group is more acidic than the aliphatic OH group and would react faster with the diethylzinc, opening the possibility to form other complexes. Diol (+)-**21** which differs from (+)-**18** only by the trifluoromethoxy group gave the (*R*)-enantiomer in only 50% ee and 43% yield (Entry 4). The electron-withdrawing trifluoromethyl group would make the electrons on the side chain oxygen less available for coordination to Zn compared to the methyl group resulting in a weaker coordination, which might be the reason that the lower yield and ee were observed.

C_2 symmetric ligands or catalysts can reduce the number of competing diastereomeric transition state structures by a factor of two and hence give better stereochemical control when compared to closely related C_1 symmetric derivatives. On the basis of this, we included some C_2-symmetric diols in the study. While the C_2-symmetric *o*-anisyl-BODOL (−)-**29** was a poor catalyst compared to its C_1-symmetric analogue (−)-**26**, the opposite applied to the C_2-symmetric phenyl-BODOL (−)-**30**, which gave the same yield as the C_1-symmetric catalyst (−)-**27**, but gave 38% ee compared to 18% ee (entries 11 and 12). Regarding the C_2-symmetric phenyl-BHEDOL, (−)-**7**, it was also an inefficient catalyst such as its C_1-symmetric analogue (−)-**15** (entry 13).

The diethylzinc addition in the presence of the three *o*-anisyl-substituted diols (−)-**14,** (+)-**18** and (−)-**26** and monoalcohol (+)-**22** was monitored over time (Fig. 2). We observed a much faster reaction with the 2,6-substituted catalysts (+)-**18** and (+)-**22** than with the 2,5-substituted catalysts (−)-**14** and (−)-**26**. Monoalcohol (+)-**22** gave the fastest reaction with complete conversion of the benzaldehyde after 22 h. However, as seen in Table 1, the enantioselectivity was low. Diol (+)-**18** was slower than monoalcohol (+)-**22**, but high conversion was achieved after 40 h. Both 2,5-BHEDOL (−)-**14** and 2,5-anisyl-BODOL (−)-**26** were poor catalysts and a substantial amount of benzaldehyde remained after 40 h.

Benzylalcohol is a common by-product in the diethylzinc addition, especially if the reaction is slow,[1] which we also observed in our experiments. Thus, while most reactions gave 5–8% of benzylalcohol, the fast reaction using mono alcohol (+)-**22** gave only 1%. However, two catalysts, (+)-**19** and (−)-**29** gave more benzyl alcohol, 17% and 13%, respectively, even if they had similar reactivities to many of the other catalysts. Thus, there seems to be no simple correlation between the formation of benzyl alcohol and the rate of reaction.

Since several of the tested catalysts were diols, it seemed possible that both ethyl groups of diethylzinc could be replaced by alco-

Table 1
Application of bicyclic catalysts in the addition of diethylzinc to benzaldehyde

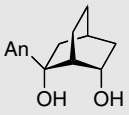
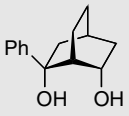
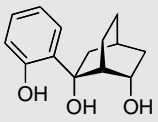
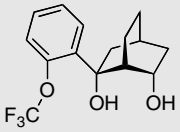
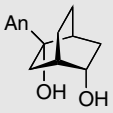
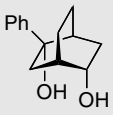
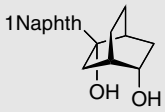
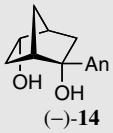
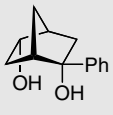
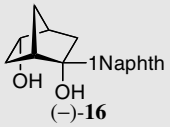
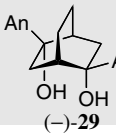
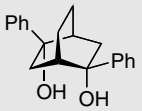
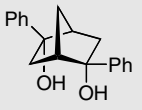
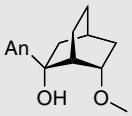
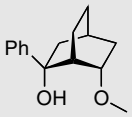
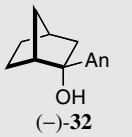
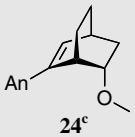
Entry	Catalyst	ee[a] of 1-phenylpropanol (%)	Yield[a] of 1-phenylpropanol (%)	Configure[b] of 1-phenylpropanol
1	 (+)-**18**	90	83	(*R*)
2	 (+)-**19**	*rac*	50	—
3	 (+)-**20**	72	69	(*S*)
4	 (+)-**21**	50	43	(*R*)
5	 (−)-**26**	82	66	(*R*)
6	 (−)-**27**	18	31	(*R*)
7	 (−)-**28**	12	50	(*R*)
8	 (−)-**14**	60	52	(*R*)
9	 (−)-**15**	2	28	(*R*)
10	 (−)-**16**	38	28	(*S*)
11	 (−)-**29**	44	29	(*R*)

Table 1 (*continued*)

Entry	Catalyst	ee[a] of 1-phenylpropanol (%)	Yield[a] of 1-phenylpropanol (%)	Configure[b] of 1-phenylpropanol
12	 (−)-**30**	38	31	(*R*)
13	 (−)-**7**	6	19	(*S*)
14	 (+)-**22**	26–44	97	(*R*)
15	 (+)-**23**	18	16	(*R*)
16	 (−)-**32**	4	17	(*S*)
17	 **24**[c]	*rac*	17	(*S*)

[a] Determined by GC analysis using a chiral Supelco betaDEX column. The yields were calculated by the use of 1-decanol as internal standard.
[b] Determined by the order of elution on the Supelco betaDEX column.
[c] The specific rotation of **24** was not recorded.

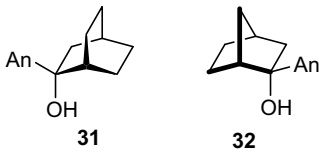

31 **32**

Figure 1. Monoalcohols **31** and **32**.

holates to form 2 equiv of ethane and a cyclic dialkoxy zinc derivative. Prasad et al. showed that the cyclic zinc dialkoxide of 1,2-diphenylethane-1,2-diol, formed by heating a mixture of equimolar amount of diol and diethylzinc to 80 °C, was a more efficient catalyst in the diethylzinc addition to benzaldehyde than the zinc monoalkoxide of the same diol formed at room temperature.[20] Apparently the exchange of the second ethyl group is rather slow. To investigate if pre-heating of a mixture of our bicyclic diols and diethylzinc would have any effect on the catalytic activity, we heated a mixture of (+)-**18** (5 mol %) and diethylzinc in hexane to 70 °C for 30 min before the mixture was cooled to 0 °C after which

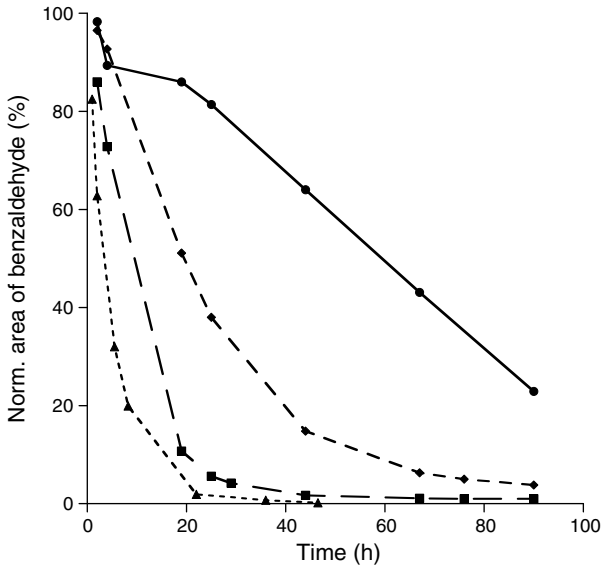


Figure 2. Diethylzinc addition monitored over time in the presence of (−)-**14** (●), (+)-**18** (■), (−)-**26** (♦) and (+)-**22** (▲).

diethyl ether and benzaldehyde were added. However, this had no effect on the yield or the enantioselectivity. We therefore assume that only one of the ethyl groups is exchanged under our ordinary conditions.

Next, the amount of diethylzinc was varied to see if it had any effect on the yield or the enantioselectivity. Equimolar amounts of diethylzinc and benzaldehyde gave a slightly lower yield than 2 equiv of diethylzinc and the ee decreased somewhat, from 90% to 86%. Two or 3 equiv of diethylzinc gave no difference in yield or ee. On the other hand, when catalyst (+)-**18** and diethylzinc were used in equimolar amounts, no product was formed. This means that a complex was formed between alkylzinc and (+)-**18** by elimination of ethane but this complex could not alkylate the benzaldehyde, despite the presence of an ethyl group bound to Zn. Nevertheless, it did catalyze the alkylation if diethylzinc was present in excess. The same observation was made for catalysis by aminoalcohols.[21]

The reaction mechanism of the diethylzinc addition to aldehydes catalyzed by aminoalcohols has been extensively studied, both experimentally and theoretically, and several types of transition states have been proposed.[4] To the best of our knowledge, no such studies have been performed on the reaction catalyzed by diols. When diethylzinc reacts with an alcohol, ethane and the ethyl-zinc alkoxide are likely to be formed. We speculate that the reaction primarily took place at the least sterically hindered secondary hydroxyl, but the zinc alkoxide formed was in equilibrium with the zinc alkoxide of the tertiary hydroxyl. The zinc alkoxide of the tertiary hydroxyl has the possibility to form the complexes shown in Figure 3, involving two tetra-coordinated Zn atoms, which would be a likely coordination for zinc alkoxides.[22] One of the zinc atoms may act as a Lewis acid and coordinate to the oxygen atom of the benzaldehyde. The other zinc atom serves to deliver the ethyl group to one of the faces of the prochiral benzaldehyde, which apparently orientates itself so as to expose its re-face towards the ethyl-zinc bond. Several other reaction sequences and transition states may be possible. In order to gain deeper insights, separate investigations are required.

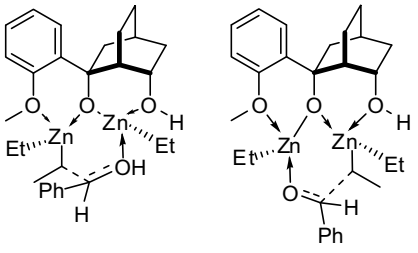


Figure 3. Suggested transition state structures of catalyst (+)-**18**, diethylzinc and benzaldehyde.

3. Conclusion

In conclusion, novel bicyclic diols have been synthesized and applied as catalysts in the diethylzinc addition to benzaldehyde. The results from this study confirm that a third coordinating site at the aryl substituent is necessary to reach high enantioselectivity. The coordination is sensitive to the distance between the coordinating groups, since 2,5-BHEDOLs and 2,5-BODOLs were inferior catalysts. A complex involving one diol, two molecules of diethylzinc and one molecule of benzaldehyde is proposed, which would explain the observations made in this investigation.

4. Experimental

4.1. General methods

All reactions were carried out in oven-dried glassware under a nitrogen atmosphere. THF and diethyl ether were distilled from sodium and benzophenone, and benzaldehyde was distilled prior to use. Anisol was filtered through a plug of neutral alumina before use. 1-Naphthylmagnesiumbromide was synthesized according to standard methods. Compounds (+)-**18**, (+)-**19**, (−)-**26**, (−)-**27**, (−)-**28**, (−)-**29** and (−)-**30**[11] were synthesized according to previous procedures. All other compounds were purchased from Aldrich and used as delivered. TLC was carried out on silica gel (60 F_{254}, Merck) and spots were visualized with UV light and then with a solution of $H_3[P(Mo_3O_{10})_4]$ (25 g), $Ce(SO_4)_2$ (10 g) and H_2SO_4 (60 mL) in H_2O (940 mL) or with a solution of *p*-methoxybenzaldehyde (10 mL), concd sulfuric acid (50 mL) and ethanol (95%, 940 mL). Flash chromatography was performed on Matrex (25–70 μm) silica gel. GC analyses were performed on a betaDEX column (Supelco, 30 m × 0.25 mm id, 25 μm film thickness). NMR spectra were recorded on a Bruker DRX 400 MHz spectrometer using the residual solvent as internal standard if not otherwise mentioned. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter at 20 °C and are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded on a Shimadzu 8300 FTIR spectrometer. Melting points were taken on a Sanyo Gallenkamp melting point apparatus (MPD.350.BM3.5) and are uncorrected. Elemental analyses were performed by H. Kolbe Mikroanalytisches Laboratorium, Höhenweg 17, D-45470 Mülheim an der Ruhr.

4.2. General procedure: addition of Et_2Zn to benzaldehyde

The catalyst (5 mol %) was dissolved in dry ether (2 mL) and diethylzinc (1.0 M in hexane, 3 mL, 3.0 mmol) was added at 0 °C. The mixture was stirred for 30 min and then freshly distilled benzaldehyde (0.10 mL, 1.0 mmol) was added. The reaction was stirred under N_2 at 0 °C for 40 h, then satd aqueous NH_4Cl was added. Dichloromethane (10 mL) was used to extract the aqueous phase on an Isolute® Phase Separator column. Yields and ee were determined by GC analysis on a Supelco betaDEX column (isothermal at 130 °C, flow rate 1 mL/min). 1-Decanol was used as internal

standard. The retention times were benzaldehyde 4.6 min, benzylalcohol 9.3 min, 1-decanol 13.7 min, (*R*)-1-phenylpropanol 14.1 min and (*S*)-1-phenylpropanol 14.8 min.

4.3. Enzymatic resolution giving (+)-(1*S*,2*R*,4*R*,5*R*,6*S*)-2-acetoxy-5,6-epoxynorbornane (+)-2 and (−)-(1*R*,2*S*,4*S*,5*S*,6*R*)-5,6-epoxy-2-norbornol (−)-3

Novozym 435 (10.15 g), followed by isopropenylacetate (17.5 mL, 158 mmol), was added to a solution of **3** (10.0 g, 80 mmol) in toluene (400 mL) at rt. MS 4 Å was added to the mixture, then it was orbitally shaken at rt for 6 h. Novozym 435 was filtered off and rinsed with toluene. The solvent was removed at reduced pressure to give a yellow oil, which was column chromatographed (SiO_2, heptane–EtOAc, 30:70) to give (+)-**2** (7.82 g, 58%, 68% ee) and (−)-**3** (3.85 g, 38%, 96% ee).

Acetate (+)-**2** (50–60% ee) was hydrolyzed by treatment with 2 M NaOH to give (+)-**3** (9.17 g, 50–60% ee) and the above procedure was repeated. The reaction was stopped after ≈4 h. Column chromatography (SiO_2, heptane–EtOAc, 30:70) gave (+)-**2** (9.22 g, 74%) of 95% ee.

4.4. (−)-(1*S*,2*S*,4*S*,5*R*)-2-Phenyl-bicyclo[2.2.1]heptane-2,5-diol (−)-9

PhMgCl (2.0 M in THF, 4.5 mL, 9 mmol) was added to a solution of (−)-**5** (0.39 g, 3.1 mmol) in dry THF (10 mL) at 0 °C under an argon atmosphere. A white precipitate was formed. The resulting slurry was stirred at rt for 1 h then satd aqueous NH_4Cl (10 mL) was added. The organic phase was collected and the aqueous phase was extracted with EtOAc (3×15 mL). The combined organic phases were washed with brine followed by drying over Na_2SO_4 and removal of the solvent at reduced pressure. The residue was recrystallized from heptane–EtOAc and the mother liquor was column chromatographed (SiO_2, heptane–EtOAc, 40:60) to give (−)-**9** (0.50 g, 82%) of 94% ee as white crystals; TLC R_f 0.4 (*i*-PrOH–CH_2Cl_2, 10:90); mp 158–163 °C; $[\alpha]_D^{20} = -20$ (*c* 1.1, EtOH); IR (KBr) 3308 cm^{-1}; ^1H NMR (400 MHz, pyridine-d_5) δ 7.81–7.83 (2H, m), 7.40–7.44 (2H, m), 7.27–7.31 (1H, m), 6.56 (1H, s), 6.10 (1H, d, *J* = 3.6 Hz), 4.48 (1H, m), 3.26–3.31 (1H, ddd, *J* = 12.7, 6.9, 2.3 Hz), 2.74 (1H, d, *J* = 3.7 Hz), 2.44–2.53 (2H, m), 2.08–2.12 (1H, dm, *J* = 9.9 Hz), 1.66–1.80 (2H, m), 1.63 (1H, m); ^{13}C NMR (100 MHz, pyridine-d_5) δ 35.2, 36.3, 43.3, 46.9, 48.1, 74.5, 79.3, 127.0, 127.4, 128.7, 151.4; HRMS (ES+) [M−OH]: calcd for $C_{13}H_{15}O$: 187.1123. Found: 187.1105. ($C_{13}H_{16}O_2$ requires C, 76.44; H, 7.90. Found: C, 76.38; H, 8.02.)

4.5. (−)-(1*S*,2*S*,4*S*,5*R*)-2-(1-Naphthyl)-bicyclo[2.2.1]heptane-2,5-diol (−)-10

The title compound was synthesized following the same procedure as for (−)-**9**, from (−)-**5** (0.3 g, 2.4 mmol) and 1 M 1-naphthylMgBr (7.1 mL, 7.1 mmol) in THF. Recrystallization from EtOAc and column chromatography of the mother liquor (SiO_2, toluene–EtOAc, 1:1) gave (−)-**10** (0.458 g, 75%) of 94% ee as white crystals; TLC R_f 0.38 (CH_2Cl_2–*i*-PrOH, 9:1); $[\alpha]_D^{20} = -91$ (*c* 2.4, EtOH); mp 187–188 °C; IR (KBr) 3362 cm^{-1}; ^1H NMR (400 MHz, pyridine-d_5) δ 9.15 (1H, d, *J* = 8.6 Hz), 7.95–7.97 (1H, m), 7.84 (1H, d, *J* = 8.1 Hz), 7.68 (1H, d, *J* = 7.2 Hz), 7.49–7.60 (2H, m), 7.45 (1H, t, *J* = 7.7 Hz), 6.75 (1H, s), 6.15 (1H, d, *J* = 3.5 Hz), 4.54–4.56 (1H, m), 3.36–3.42 (1H, m), 3.18 (1H, d, *J* = 4.1 Hz), 2.44–2.46 (1H, m), 2.38 (1H, dm, *J* = 13.1 Hz), 2.25 (1H, dm, *J* = 9.9 Hz), 2.10 (1H, dd, *J* = 13.1, 2.9 Hz), 1.86 (1H, dm, *J* = 12.8 Hz), 1.72 (1H, d, *J* = 9.7 Hz); ^{13}C NMR (100 MHz, pyridine-d_5) δ 35.7, 36.0, 45.3, 46.6, 46.7, 74.6, 79.6, 122.5, 125.4, 125.6, 126.0, 128.4, 129.5, 129.7, 133.0, 146.1 (one peak hidden by solvent); HRMS (FAB+, direct inlet) [M]: calcd for $C_{17}H_{18}O_2$: 254.1307 Found: 254.1304; ($C_{17}H_{18}O_2$ requires C, 80.26; H, 7.13. Found: C, 80.19; H, 7.18.)

4.6. (−)-(1*S*,2*S*,4*S*,5*S*)-2,5-Diphenyl-bicyclo[2.2.1]heptane-2,5-diol (−)-7

The title compound was synthesized following the same procedure as for (−)-**9**, from (−)-**6** (0.47 g, 3.8 mmol) and PhMgCl (2.0 M in THF, 9.4 mL, 19 mmol). Recrystallization from toluene and column chromatography of the mother liquor (SiO_2, pentane–diethyl ether, 6:4) gave (−)-**7** (0.63 g, 63%) of 97% ee as white crystals. The ^1H NMR analysis was in accordance with literature.[10]

4.7. (−)-(1*S*,2*S*,4*S*,5*R*)-2-(2-Methoxy-phenyl)-bicyclo[2.2.1]-heptane-2,5-diol (−)-8

n-BuLi (2.5 M in hexane, 2.5 mL, 6.3 mmol) was added dropwise to a solution of anisol (0.70 mL, 6.5 mmol) in dry THF (23 mL) at −70 °C. The resulting solution was allowed to warm to 0 °C and stirred for at least 30 min. Then (−)-**5** (0.30 g, 2.4 mmol) dissolved in THF (4 mL) was added. The resulting slurry was stirred at rt for 2 h followed by the addition of sat. aqueous NH_4Cl (20 mL). The mixture was worked up as follows: extraction with EtOAc (3 × 20 mL), washing of the collected organic phases with satd aqueous $NaHCO_3$ and brine followed by drying over Na_2SO_4 and removal of the solvent at reduced pressure. The crude product was column chromatographed (SiO_2, CH_2Cl_2–*i*-PrOH, 95:5) followed by recrystallization from toluene to give (−)-**8** (0.36 g, 65%) in 94% ee as white crystals; TLC R_f 0.6 (CH_2Cl_2–*i*-PrOH, 90:10); mp 127–129 °C; $[\alpha]_D^{20} = -15$ (*c* 1.1, $CHCl_3$); IR (KBr) 3300 cm^{-1}; ^1H NMR (400 MHz, pyridine-d_5) δ 7.48–7.50 (1H, m), 7.28–7.32 (1H, m), 6.98–7.05 (2H, m), 6.05 (1H, d, *J* = 3.6 Hz), 5.01 (1H, s), 4.41–4.43 (1H, m), 3.73 (3H, s), 3.19–3.24 (1H, ddd, *J* = 12.8, 6.9, 2.3 Hz), 2.95–2.96 (1H, m), 2.44–2.45 (1H, m), 2.29–2.34 (1H, m), 2.11–2.14 (1H, dm, *J* = 9.9 Hz), 1.70–1.78 (2H, m), 1.55–1.57 (1H, dm, *J* = 9.9 Hz); ^{13}C NMR (100 MHz, pyridine-d_5) δ 35.4, 35.7, 43.9, 45.8, 46.6, 55.7, 74.5, 79.0, 112.6, 121.0, 126.2, 128.7, 137.3, 158.6; HRMS (FAB+, direct inlet) [M]: calcd for $C_{14}H_{18}O_3$: 234.1256. Found: 234.1253. ($C_{14}H_{18}O_3$ requires C, 71.77; H, 7.74. Found: C, 71.72; H, 7.70.)

4.8. (+)-(1*R*,2*R*,4*S*,6*S*)-2-(2-Trifluoromethoxy-phenyl)-bicyclo[2.2.2]octane-2,6-diol (+)-21

Trifluoromethoxybenzene (0.83 mL, 6.3 mmol) and TMEDA (0.94 mL, 6.3 mmol) were dissolved in dry THF (13 mL) and cooled to −78 °C. *sec*-BuLi (1.4 M in cyclohexane, 4.5 mL, 6.3 mmol) was added and the resulting yellow solution was stirred at −78 °C for 3.5 h. Then (−)-**17** dissolved in THF (8 mL) was added and the reaction was allowed to reach rt. After 1 h water (20 mL) was added and the aqueous phase was extracted with diethyl ether (3×30 mL). The combined organic phases were washed with brine followed by drying over Na_2SO_4 and removal of the solvent at reduced pressure. The residue was column chromatographed (SiO_2, heptane–EtOAc, 70:30) to give (+)-**21** (0.43 g, 68%) of >99% ee as yellow crystals. TLC R_f 0.51 (heptane–EtOAc, 1:1); $[\alpha]_D^{20} = +60$ (*c* 0.9, $CHCl_3$); mp 73–75 °C; IR (NaCl) 3308 cm^{-1} (very broad); ^1H NMR (400 MHz, C_6D_6) δ 0.85–1.00 (2H, m), 1.14–1.19 (2H, m), 1.54–1.59 (1H, m), 1.63–1.68 (1H, m), 1.87 (1H, dt, *J* = 14.4, 2.0 Hz), 1.99–2.06 (1H, m), 2.22–2.26 (1H, m), 1.34 (1H, m), 3.21 (1H, s), 3.38 (1H, d, *J* = 9.2 Hz), 3.80–3.86 (1H, m), 6.76–6.84 (2H, m), 7.02–7.04 (1H, m), 7.10–7.13 (1H, m); ^{13}C NMR (100 MHz, C_6D_6) δ 21.6, 23.6, 26.3, 37.8, 39.5, 44.3, 70.8, 76.6, 120.3, 122.9, 126.1, 127.9, 129.0, 138.6, 149.4; HRMS (FAB+) [M+Na]: calcd for $C_{15}H_{17}O_3F_3Na$: 325.1027. Found:

325.1031; ($C_{15}H_{17}O_3F_3$ requires C, 59.60; H, 5.67. Found: C, 59.49; H, 5.61.)

4.9. (+)-(1*R*,2*R*,4*S*,6*S*)-2-(2-Hydroxy-phenyl)-bicyclo[2.2.2]-octane-2,6-diol (+)-20

2-Bromophenol (0.73 mL, 6.3 mmol) was added to a solution of *n*-BuLi (2.5 M in hexane, 5.0 mL, 12.6 mmol) in diethyl ether (15 mL) at −78 °C. The colourless mixture was stirred at rt for 3.5 h, then cooled to −78 °C followed by the addition of (−)-**17** (0.30 g, 2.1 mmol) dissolved in diethyl ether (20 mL). After 3 h, satd aqueous NH_4Cl was added to the yellow solution. The aqueous phase was saturated with NaCl and then extracted with diethyl ether. The combined organic phases were washed with brine followed by drying over Na_2SO_4 and removal of the solvent at reduced pressure. The residue was column chromatographed (SiO_2, heptane–EtOAc 80:20) to give (+)-**20** (0.17 g, 35%) of >99% ee as a very viscous oil; TLC R_f 0.49 (heptane–EtOAc, 1:1); $[\alpha]_D^{20} = +38$ (*c* 0.56, $CHCl_3$); IR (NaCl) 3308 (very broad) cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.60–0.69 (1H, m), 0.76–0.83 (1H, m), 1.00–1.13 (2H, m), 1.25–1.31 (1H, m), 1.48–1.52 (1H, m), 1.59–1.67 (1H, m), 1.77 (1H, dt, *J* = 12.4, 2.8 Hz), 1.99–2.01 (1H, m), 2.42 (1H, dt, *J* = 15.2, 2.8 Hz), 3.44–3.49 (1H, m), 6.15 (1H, s), 6.76–6.80 (1H, m), 6.95–6.97 (1H, m), 7.10–7.14 (1H, m), 7.20–7.22 (1H, m), 10.29 (1H, s); ^{13}C NMR (100 MHz, C_6D_6) δ 20.4, 22.5, 26.1, 37.8, 39.7, 42.8, 71.7, 80.4, 119.0, 119.1, 127.4, 129.3, 129.8, 158.8; HRMS (FAB+) [M+Na]: calcd for $C_{14}H_{18}O_3Na$: 257.1154. Found: 257.1154; ($C_{14}H_{18}O_3$ requires C, 71.77; H, 7.74. Found: C, 71.83; H, 7.80.)

4.10. (−)-(1*S*,4*S*,5*S*)-5-Hydroxy-5-phenyl-bicyclo[2.2.1]heptan-2-one (−)-12

Compound (−)-**9** (0.50 g, 2.4 mmol), NMO (0.56 g, 4.8 mmol), MS 4 Å and TPAP (0.042 g, 0.12 mmol) were mixed in CH_2Cl_2 (50 mL). The resulting mixture was stirred at rt for 1.5 h, then diluted with EtOAc and filtered through Celite/silica (rinsed with EtOAc). The solvent was removed at reduced pressure and the resulting oil was filtered through a pad of SiO_2 (heptane–EtOAc, 1:1) to give (−)-**12** (0.44 g, 91%) of 94% ee as a white solid. Recrystallization from toluene gave >99% ee; TLC R_f 0.44 (heptane–EtOAc, 1:1); $[\alpha]_D^{20} = -56$ (*c* 1.1, $CHCl_3$); mp 101–103 °C; IR (KBr) 3365, 1720 cm^{-1}; ^1H NMR (400 MHz, pyridine-d_5) δ 7.75–7.78 (2H, m), 7.42–7.45 (2H, m), 7.30–7.34 (1H, m), 7.18 (1H, s), 3.23–3.29 (1H, dd, *J* = 17.5, 4.3 Hz), 2.95 (1H, m), 2.63–2.70 (2H, m), 2.09–2.19 (2H, m), 1.82–1.85 (1H, m), 1.66–1.69 (1H, m); ^{13}C NMR (100 MHz, pyridine-d_5) δ 38.4, 41.3, 44.1, 48.5, 53.2, 79.9, 128.0, 128.4, 129.9, 218.2 (one peak hidden by solvent); HRMS (ES+) [M+H]: calcd for $C_{13}H_{15}O_2$: 203.1072. Found: 203.1069; ($C_{13}H_{14}O_2$ requires C, 77.20; H, 6.98. Found: C, 77.33; H, 6.91.)

4.11. (−)-(1*S*,4*S*,5*S*)-5-Hydroxy-5-(1-naphthyl)-bicyclo[2.2.1]-heptan-2-one (−)-13

The title compound was synthesized from (−)-**10** (0.30 g, 1.2 mmol) following the same procedure as for (−)-**12**. The resulting solid was column chromatographed (SiO_2, heptane–EtOAc, 1:1) to give (−)-**13** (0.27 g, 83%) of 94% ee as a white solid. Recrystallization from heptane–EtOAc gave >99% ee; TLC R_f 0.46 (heptane–EtOAc, 1:1); $[\alpha]_D^{20} = -119$ (*c* 1.15, *t*-BuOMe); mp 144–147 °C; IR (KBr) 3447, 3071, 1728 cm^{-1}; ^1H NMR (400 MHz, pyridine-d_5) δ 9.03 (1H, d, *J* = 8.4 Hz), 7.96–7.99 (1H, m), 7.88 (1H, d, *J* = 8.1 Hz), 7.51–7.61 (3H, m), 7.46 (1H, t, *J* = 7.7 Hz), 7.36 (1H, s), 3.44 (1H, d, *J* = 3.4 Hz), 3.37 (1H, dd, *J* = 17.6, 4.1 Hz), 2.63 (1H, br s), 2.51 (2H, m), 2.26 (1H, dd, *J* = 17.5, 4.7 Hz), 1.86–1.90 (1H, dm, *J* = 10.6 Hz), 1.81 (1H, d_{AB}, J_{AB} = 10.6 Hz); ^{13}C NMR (100 MHz, pyridine-d_5) δ 37.8, 40.2, 44.6, 46.1, 52.2, 79.4, 122.3, 125.5, 126.1, 126.3, 129.0, 129.3, 129.7, 132.7, 144.8, 217.3 (one peak hidden by solvent); HRMS (FAB+, direct inlet) [M]: calcd for $C_{17}H_{16}O_2$: 252.1150. Found: 252.1156; ($C_{17}H_{16}O_2$ requires C, 80.93; H, 6.39. Found: C, 80.79; H, 6.43.)

4.12. (−)-(1*S*,4*S*,5*S*)-5-Hydroxy-5-(2-methoxy-phenyl)-bicyclo[2.2.1]heptan-2-one (−)-11

The title compound was synthesized from (−)-**8** (2.33 g, 10 mmol) following the same procedure as for (−)-**12**. The resulting solid was column chromatographed (SiO_2, heptane–EtOAc, 70:30) to give (−)-**11** (1.98 g, 85%) of 96% ee as a white solid. Recrystallization from heptane–EtOAc gave 99% ee; TLC R_f 0.42 (heptane–EtOAc, 1:1); $[\alpha]_D^{20} = -64$ (*c* 1, $CHCl_3$); mp 112.9–113.4 °C; IR (KBr) 3535, 3507, 1748 cm^{-1}; ^1H NMR (400 MHz, pyridine-d_5) δ 7.42–7.44 (1H, m), 7.31–7.35 (1H, m), 6.99–7.06 (2H, m), 5.62 (1H, s), 3.70 (3H, s), 3.24 (1H, m), 3.17–3.22 (1H, dd, *J* = 17.5, 3.5 Hz), 2.60–2.61 (1H, m), 2.43–2.48 (1H, m), 2.13–2.23 (2H, m), 1.69–1.76 (1H, m); ^{13}C NMR (100 MHz, pyridine-d_5) δ 37.5, 39.9, 44.1, 44.9, 52.3, 55.7, 78.4, 112.7, 121.1, 125.6, 129.2, 158.6, 217.3 (one peak hidden by solvent); HRMS (ES+) [M−OH]: calcd for $C_{14}H_{15}O_2$: 215.1072. Found: 215.1067; ($C_{14}H_{16}O_3$ requires C, 72.39; H, 6.94. Found: C, 72.42; H, 7.06.)

4.13. (−)-(1*S*,2*S*,4*S*,5*S*)-2-Phenyl-bicyclo[2.2.1]heptane-2,5-diol (−)-15

$NaBH_4$ (0.056 g, 1.5 mmol) was added in portions at 0 °C to a solution of (−)-**12** (0.1 g, 0.5 mmol) in MeOH (10 mL). The resulting solution was stirred at 0 °C for 15 min then water (5 mL) was added. The aqueous phase was extracted with EtOAc, the combined organic phases were washed with brine, dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was column chromatographed (SiO_2, *i*-PrOH–CH_2Cl_2, 10:90) to give (−)-**15** (0.090 g, 88%) of >99% ee as a white solid. TLC R_f 0.19 (heptane–EtOAc, 1:1); $[\alpha]_D^{20} = -23$ (*c* 0.6, EtOH); mp 71–72 °C; IR (KBr) 3457, 3377, 3296 cm^{-1}; ^1H NMR (400 MHz, pyridine-d_5) δ 7.83–7.84 (2H, m), 7.41–7.45 (2H, m), 7.27–7.31 (1H, m), 4.58–4.63 (1H, m), 2.93 (1H, dd, *J* = 13.2, 3.0 Hz), 2.68 (1H, dt, *J* = 12.8, 3.3 Hz), 2.61–2.62 (1H, m), 2.47 (1H, m), 2.34 (1H, dd_{AB}, *J* = 13.2, 4.9 Hz), 1.97–2.04 (1H, m), 1.69 (1H, dm_{AB}, J_{AB} = 10.7 Hz), 1.41 (1H, dm_{AB}, J_{AB} = 10.4 Hz); ^{13}C NMR (100 MHz, pyridine-d_5) δ 33.4, 37.7, 37.7, 44.8, 49.7, 72.5, 80.4, 127.0, 127.4, 128.8 (one peak hidden by solvent); HRMS (ES+) [M+H]: calcd for $C_{13}H_{16}O_2$: 204.1150. Found: 204.1169; ($C_{13}H_{16}O_2$ requires C, 76.44; H, 7.90. Found: C, 76.40; H, 7.81.)

4.14. (−)-(1*S*,2*S*,4*S*,5*S*)-2-(2-Methoxy-phenyl)-bicyclo[2.2.1]-heptane-2,5-diol (−)-14

The title compound was synthesized from (−)-**11** (0.050 g, 0.22 mmol) following the same procedure as for (−)-**15**. The crude product (−)-**14** (0.051 g, 98%) of >99% ee (white solid) was pure enough to be used without further purification; TLC R_f 0.13 (heptane–EtOAc, 1:1); $[\alpha]_D^{20} = -28$ (*c* 0.55, EtOH); mp 114–117 °C; IR (KBr) 3545, 3465 cm^{-1}; ^1H NMR (400 MHz, pyridine-d_5) δ 7.46–7.42 (1H, m), 7.32–7.28 (1H, m), 7.04–6.98 (1H, m), 5.98 (1H, br s), 4.62–4.58 (1H, m), 3.70 (3H, s), 3.01 (1H, dd, *J* = 13.6, 2.9 Hz), 2.84 (1H, d, *J* = 4.7 Hz), 2.68 (1H, dt, *J* = 12.7, 3.6 Hz), 2.39 (1H, m), 2.21 (1H, dd, *J* = 13.6, 4.9 Hz), 2.05–1.97 (1H, m), 1.62 (1H, dm_{AB}, J_{AB} = 10.2 Hz), 1.46 (1H, dm_{AB}, J_{AB} = 10.4 Hz); ^{13}C NMR (100 MHz, pyridine-d_5) δ 32.5, 37.6, 37.9, 44.6, 47.2, 55.7, 72.8, 80.2, 121.0, 123.3, 126.2, 128.6, 137.8,

158.5; HRMS (FAB+, direct inlet) [M]: calcd for $C_{14}H_{18}O_3$: 234.1256. Found: 234.1259; ($C_{14}H_{18}O_3$ requires C, 71.77; H, 7.74. Found: C, 71.87; H, 7.68.)

4.15. (−)-(1*S*,2*S*,4*S*,5*S*)-2-(1-Naphthyl)-bicyclo[2.2.1]heptane-2,5-diol (−)-16

The title compound was synthesized following the same procedure as for (−)-**15** from (−)-**13** (0.1 g, 0.4 mmol) to give (−)-**16** (0.080 g, 79%) of >99% ee as a white solid; TLC R_f 0.24 (heptane–EtOAc, 1:1); $[\alpha]_D^{20} = -68$ (*c* 1.1, EtOH); mp 155–157 °C; IR (KBr) 3320, 3251 cm^{-1}; ^1H NMR (400 MHz, pyridine-d_5) δ 9.26 (1H, m), 7.97–7.95 (1H, m), 7.85 (1H, d, *J* = 8.1 Hz), 7.61 (1H, d, *J* = 7.3 Hz), 7.58–7.43 (3H, m), 4.68–4.64 (1H, m), 3.39 (1H, dd, *J* = 13.0, 2.8 Hz), 3.07 (1H, d, *J* = 4.5 Hz), 2.84 (1H, dt, *J* = 12.9, 3.4 Hz), 2.38 (1H, m), 2.29 (1H, dd_{AB}, *J* = 12.9, 4.7 Hz), 2.15-2.08 (1H, m), 1.77 (1H, dm_{AB}, J_{AB}=10.1 Hz), 1.57 (1H, dm_{AB}, J_{AB} = 10.1 Hz); ^{13}C NMR (100 MHz, pyridine-d_5) δ 146.6, 132.9, 129.9, 129.6, 128.4, 126.0, 125.6, 125.5, 122.4, 80.8, 72.7, 48.2, 44.6, 39.6, 38.0, 32.8; HRMS (FAB+, direct inlet) [M]: calcd for $C_{17}H_{18}O_2$: 254.1307. Found: 254.1302; (The compound did not pass elemental analysis due to remaining *i*-PrOH despite prolonged pumping under vacuum.)

4.16. (+)-(1*R*,2*R*,4*S*,6*S*)-6-Methoxy-2-(2-methoxy-phenyl)-bicyclo[2.2.2]octan-2-ol (+)-22

Powdered KOH (0.33 g, 6.6 mmol) was added to a solution of (+)-**18** (0.80 g, 3.2 mmol) and MeI (2.0 mL, 32 mmol) in THF (15 mL). The mixture was stirred at rt over night. Then water (15 mL) was added. The phases were separated and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with brine, dried over Na_2SO_4 and the solvent was removed at reduced pressure. The crude product was purified by column chromatography (SiO_2, heptane–EtOAc, 75:25) giving compound (+)-**22** as a white solid (0.74 g, 88%, >99% ee). TLC R_f 0.43 (heptane–EtOAc, 1:1); $[\alpha]_D^{20} = +67$ (*c* 1.5, $CHCl_3$); mp 73–77 °C; IR (KBr) 3540 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.04–1.14 (1H, m), 1.18–1.25 (1H, m), 1.31–1.42 (1H, m), 1.79–1.82 (1H, m), 1.85–1.93 (1H, m), 2.01–2.07 (1H, m), 2.30–2.35 (1H, m), 2.38–2.42 (1H, m), 2.67–2.68 (1H, m), 3.13 (3H, s), 3.33 (3H, s), 3.36–3.43 (1H, m), 4.95 (1H, s), 6.62–6.64 (1H, m), 6.89–6.93 (1H, m), 7.06–7.13 (1H, m), 7.36–7.42 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 24.4, 26.6, 34.3, 37.4, 41.3, 55.6, 56.0, 76.2, 81.2, 113.4, 120.8, 127.4, 128.3, 136.0, 159.6; HRMS (FAB+, direct inlet) [M]: calcd for $C_{16}H_{22}O_3$: 262.1569. Found: 262.1569. The compound did not pass elemental analysis due to elimination of water upon standing.

4.17. (+)-(1*R*,2*R*,4*S*,6*S*)-6-Methoxy-2-phenyl-bicyclo[2.2.2]-octan-2-ol (+)-23

The title compound was synthesized by following the same procedure as for (+)-**22** starting from (+)-**19** (0.45 g, 2.0 mmol). The crude product was purified by column chromatography (SiO_2, heptane–EtOAc, 95:5) giving compound (+)-**23** as white solid (0.38 g, 80%, >99% ee); TLC R_f 0.72 (heptane–EtOAc, 1:1); $[\alpha]_D^{20} = +60$ (*c* 1.1, $CHCl_3$); mp ≈20 °C; IR (KBr) 3455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.76–0.84 (1H, m), 0.99–1.02 (1H, m), 1.14–1.24 (1H, m), 1.26–1.34 (1H, m), 1.58–1.64 (1H, m), 1.66–1.76 (2H, m), 1.89–1.91 (1H, m), 2.07 (1H, dt, *J* = 2.8, 14.8 Hz), 2.42 (1H, dt, *J* = 2.8, 14.8 Hz), 2.96 (3H, s), 3.20–3.24 (1H, m), 5.62 (1H, s), 7.11–7.19 (1H, m), 7.27–7.31 (1H, m), 7.72–7.75 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 23.5, 26.5, 35.1, 40.1, 43.7, 56.0, 75.5, 81.3, 127.1, 127.4, 128.3, 148.7; HRMS (FAB+, direct inlet) [M+Na]: calcd for $C_{15}H_{20}NaO_2$: 255.1361. Found: 255.1360. ($C_{15}H_{20}O_2$ requires C, 77.55; H, 8.68. Found: C, 77.45; H, 8.62.)

References

1. Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 34–48.
2. Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833–856.
3. Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824.
4. Martinez, A. G.; Vilar, E. T.; Fraile, A. G.; de la Moya Cerero, S.; Martinez Ruiz, P.; Diaz Morillo, C. *Tetrahedron: Asymmetry* **2007**, *18*, 742–749 and references cited therein.
5. Sarvary, I.; Wan, Y.; Frejd, T. *J. Chem. Soc., Perkin Trans. 1* **2002**, 645–651 and references cited therein.
6. Zhang, Y.-L.; Zhang, F.; Tang, W.-J.; Wu, Q.-L.; Fan, Q.-H. *Synlett* **2006**, 1250–1254.
7. Huang, W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1998**, *63*, 1364–1365.
8. Toivonen, H. *Suom. Kemistil. B* **1958**, *31B*, 354–357.
9. Weissfloch, A.; Azerad, R. *Bioorg. Med. Chem.* **1994**, *2*, 493–500.
10. Cai, C.-L.; Xia, C.-G. *Synthesis* **2006**, 2297–2300.
11. Friberg, A.; Sarvary, I.; Wendt, O.; Frejd. T. In manuscript: Bicyclo[2.2.2]octane derived chiral ligands—synthesis and application of BODOLs in the asymmetric reduction of acetophenone with catecholborane.
12. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440–467.
13. Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. 1. p 1179.
14. Fürst, A.; Koller, F. *Helv. Chim. Acta* **1947**, *30*, 1947.
15. Hutchins, R. O.; Kandasamy, D.; Dux, F., III; Maryanoff, C. A.; Rotstein, D.; Goldsmith, B.; Burgoyne, W.; Cistone, F.; Dalessandro, J.; Puglis, J. *J. Org. Chem.* **1978**, *43*, 2259–2267.
16. Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098–5100.
17. Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26–31.
18. Hatch, R. P.; Shringarpure, J.; Weinreb, S. M. *J. Org. Chem.* **1978**, *43*, 4172–4177.
19. Caglioti, L. *Org. Synth.* **1988**, *Coll. Vol. 6*, 62.
20. Prasad, K. R. K.; Joshi, N. N. *Tetrahedron: Asymmetry* **1996**, *7*, 1957–1960.
21. Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071–6072.
22. Wilkinson, G.; Stone, F. G. A.; Abel, E. W. *Comprehensive Organometallic Chemistry*; Pergamon Press, 1982. p 837.