Novel, cyclic and bicyclic 1,3-diols as catalysts for the diethylzinc addition to aldehydes

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Received (in Cambridge, UK) 5th November 2001, Accepted 25th January 2002
First published as an Advance Article on the web 11th February 2002

A number of optically pure 1,3-diols have been synthesized and used as catalysts in the asymmetric addition of diethylzinc to aromatic aldehydes. Enantiomeric excesses of up to 92% of (*R*)-1-phenylpropan-1-ol were obtained with anisylbicyclo[2.2.2]octanediol (**14**) as a catalyst. Using 2-picolylbicyclo[2.2.2]ocatanediol (**16**) as the catalyst resulted in a reversal of the stereoselectivity, yielding (*S*)-1-phenylpropan-1-ol in 83% ee. A pronounced positive non-linear effect was observed when varying the enantiomeric purity of catalyst **14**.

Introduction

The asymmetric addition of diethylzinc to aromatic aldehydes is a convenient test reaction for novel catalysts and several highly efficient catalysts based on amino alcohols and diols have been found for this reaction. Both classes of compounds have been used with and without extra metals, such as Ti(IV). The amino alcohols are most frequently used as catalysts without addition of extra metals, while in most diol cases Ti(IV) has been used to form titanate catalysts to obtain high yields and ees. Without the use of Ti(IV)-coordination the diols themselves often show lower catalytic activity and selectivity.[1,2]

Besides the addition of alkylzinc to aldehydes, bicyclic amino alcohols have been reported to be efficient catalysts for the diethylzinc addition to imines.[3] Recent developments with the reagent have enabled highly selective addition of diphenylzinc to aldehydes.[4]

One of the better diol catalysts is the diphenylglycol **1** (Fig. 1). In comparison, TADDOL (**2**) produced only moderate ees. Also, BINOL (**3**) alone or derivatives thereof, such as **4**, were poor catalysts in the diethylzinc addition to benzaldehyde.[5–7] However, coordinating ether moieties attached to the BINOL framework gave better catalysts as exemplified by **5** and dendrimers based on that subunit.[8] Other systems, including polymeric materials, showed even better enhancement, see below. The use of coordinating alkoxy groups has also been used in bicyclic diol catalysts such as **6**.[9] In contrast, the use of coordinating 2-pyridyl groups, as in **7** and **8**, reduced the selectivity substantially in comparison with **1**.[10,11]

Compound **9**, despite its coordinating diaryl ether link, gave only low ees, although it has only been investigated in autocatalytic reactions (with the corresponding dialdehyde as the aldehyde component) and is therefore a somewhat different case.[12] Some sugar derivatives have also been investigated, such as modified β-cyclodextrines and catalysts derived from D-mannitol (**10**). However, these were poor catalysts in the diethylzinc addition to aldehydes.[13,14]

Recent developments with BINOL derivatives by Pu and coworkers[15] have shown that extra, bulky and coordinating ether groups, increase catalytic efficiency. Some of these BINOL derivatives, both polymers and monomers (**12a** and **12b**, Fig. 2), show a dramatic increase in reactivity and selectivity. Thus, **12a** gave 98% ee and **12b** 99% ee in the diethylzinc addition to benzaldehydes and worked excellently in other reactions as well. In addition, similar BINOL derivatives have been anchored to

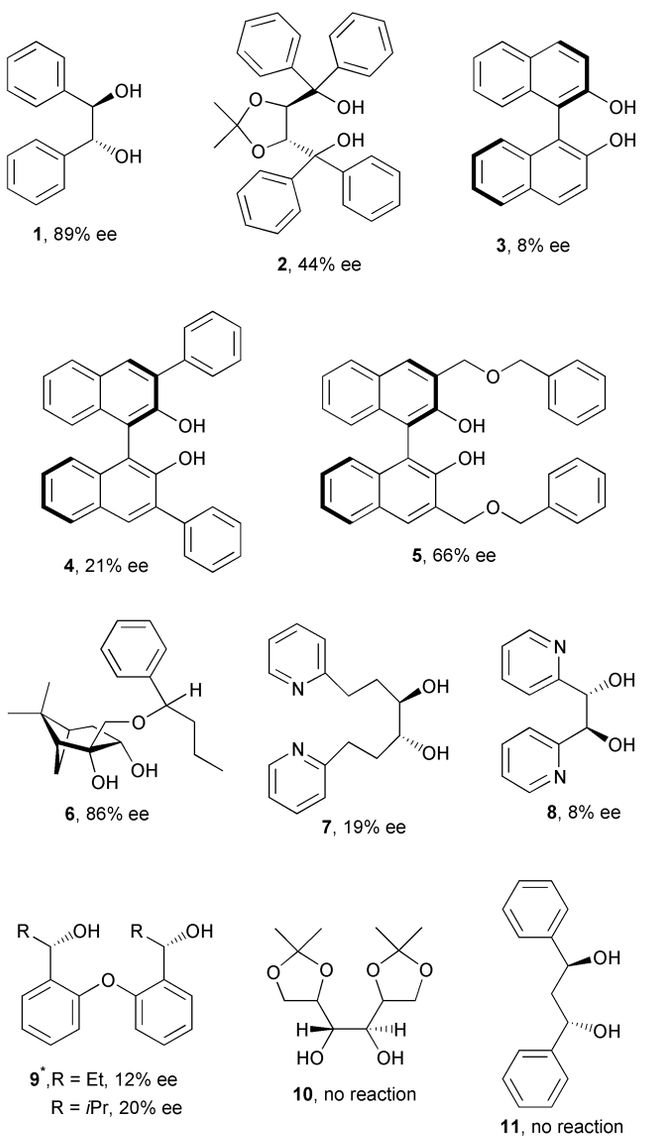


Fig. 1 Diols used as catalysts (without the use of $Ti(OPr^i)_4$) for the asymmetric addition of Et_2Zn to benzaldehyde. * denotes only used in autocatalytic reactions where the corresponding dialdehyde was used as substrate.

DOI: 10.1039/b110082n

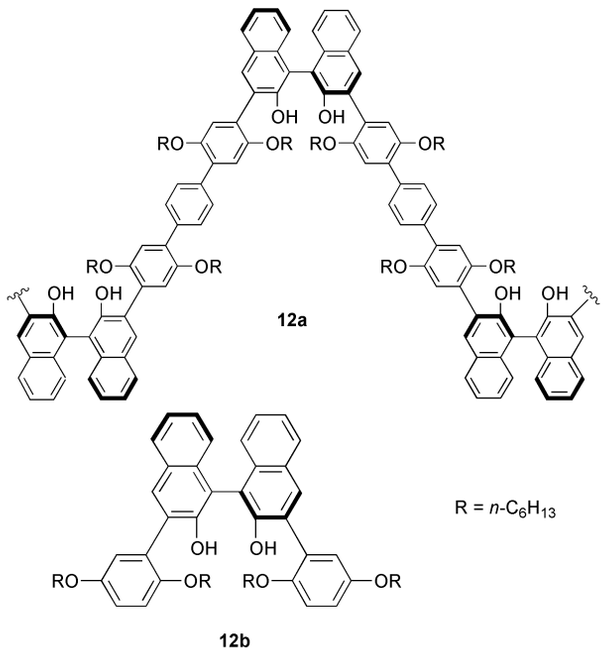


Fig. 2 A chiral BINOL polymer (**12a**) and a BINOL derivative (**12b**) used as a catalyst, Pu and co-workers.[15]

polystyrene residues and used with good results in the diethylzinc addition.[16]

Interestingly, the extra coordinating sites do not have to be incorporated into the diols to increase their catalytic ability. Large increases of both activity and selectivity, for BINOL, and derivatives thereof, were achieved by Mikami and co-workers[17] in the diethylzinc addition by adding chiral diimines such as **13** (Fig. 3) as activators. For example, a combination of **4** and **13**

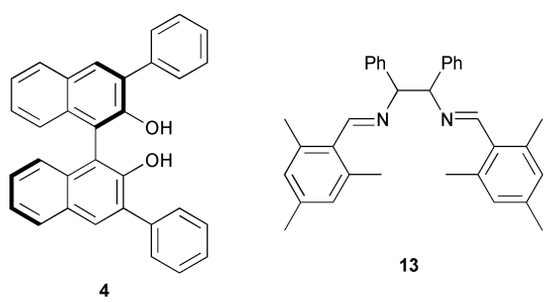


Fig. 3 The most efficient combination of BINOL derivative (**4**) and diimine activator (**13**), used by Mikami and co-workers.[17]

(10 mol% of each) resulted in 99% ee in the diethylzinc addition to benzaldehyde.

From the cases reported in the literature it seems that among the diols only 1,2- and 1,4-diols have been found to act as catalysts. To our knowledge, only one 1,3-diol (**11**) has been examined as a catalyst, although without exhibiting any catalytic effect.[6] We asked ourselves whether the 1,3-diols in general were useless as catalysts in these types of reactions. This question was all the more of interest to us, as the 1,3-diol **14** (anisyl-BODOL† ‡) was an efficient ligand in the titanium catalysed asymmetric reduction of ketones with catecholborane.[18,19]

In this report we demonstrate that the BODOLs themselves may act as catalysts in the diethylzinc addition to aldehydes. It is also shown that 1,3-diols lacking the rigidity of the bicyclic backbone were less efficient.

† We suggest that the diols based upon the bicyclo[2.2.2]octane framework be named BODOLs (*b*icyclo[2.2.2]*o*ctane-*di*o*l*s).
‡ The IUPAC name for anisyl is methoxyphenyl.

Results and discussion

In the BODOLs the coordinating hydroxy groups are positioned at a very defined distance from each other and also in relation to the rest of the molecule, due to the rigid bicyclic framework. By removing the ethylene bridge the importance of this fixation should be revealed. We therefore included the cyclohexane-1,3-diol derivatives **19** and **20** in this investigation.

We were also interested in where to place an attachment group in the BODOLs if these ligands/catalysts were to be covalently anchored to a solid phase. Two obvious positions were at the bridgeheads, which led to **17** and **18** as test substances. Moreover, these were reasonable comparison objects to **19** and **20**, with respect to the possible influence of the *gem*-dimethyl grouping. Thus, compounds **14**–**20** were tested as catalysts in the diethylzinc addition to a number of aldehydes.

First, the choice of solvents had to be made. In either toluene or mixtures of diethyl ether–hexane (2 : 3) we obtained good results. Not surprisingly, the coordinating ability of THF interfered with the complex(es) formed between the diols and diethylzinc. This resulted in loss of catalytic activity (even at THF levels below 10% in hexane) since only small amounts of phenylpropan-l-ol (<10%) formed.

The best compromise was to perform the reactions at 0 °C. At this temperature the yield and ee were 89% and 92% respectively. At −20 °C the yield was much lower (42%) and the ee was only 2% better then at 0 °C. Moreover, the reaction time was very long. At room temperature the yield was good (93%) but now the ee was lowered to 72%. We therefore chose to run the remaining catalytic reactions at 0 °C for 40 h.

As shown, the use of **14** (Fig. 4) as a catalyst in diethyl ether–

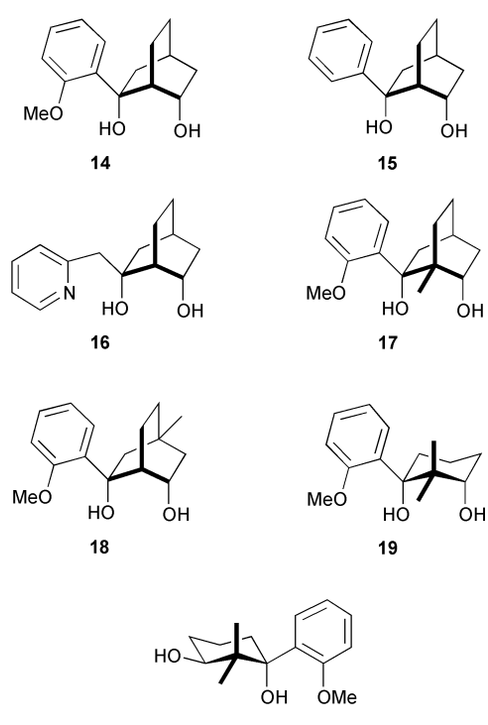
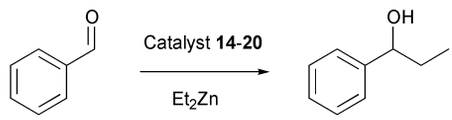
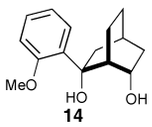
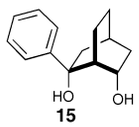
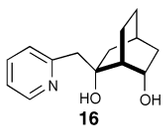
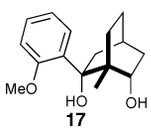
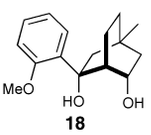
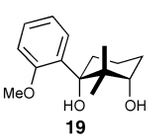
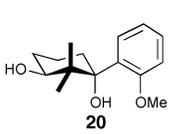


Fig. 4 The 1,3-diols used in this investigation.

hexane gave a fair yield and good ee of (*R*)-1-phenylpropan-1-ol (Table 1, entry 1A). Changing the solvent to toluene lowered both the ee and the yield somewhat (entry 1B). The necessity of an extra coordinating site in the catalyst was demonstrated in compound **15**, in which such coordination was lacking and which gave a racemic product in low yields independent of the solvent (entries 1C and 1D). We found slightly more 1-phenylpropan-1-ol when using **15** as a catalyst, compared with the background reaction (7%, in hexane–Et_2O after 42 h). To investigate autocatalysis we used the following experiment.

Table 1 Addition of diethylzinc to benzaldehyde using catalysts **14**–**20**



Entry	Catalyst	Solvent[a]	Ee[b] (%)	Yield[c] (%)	Config.[d]
1A	 **14**	Hexane–Et_2O	92	89	*R*
1B		Toluene	80	84	*R*
1C	 **15**	Hexane–Et_2O	–	17	–
1D		Toluene	–	12	–
1E	 **16**	Hexane–Et_2O	83	80	*S*
1F		Toluene	82	65	*S*
1G	 **17**	Hexane–Et_2O	28	27	*S*
1H		Toluene	46	39	*S*
1I	 **18**	Hexane–Et_2O	89	85	*R*
1J		Toluene	56	76	*R*
1K	 **19**	Hexane–Et_2O	40	34	*S*
1L		Toluene	61	26	*S*
1M	 **20**	Hexane–Et_2O	16	25	*S*
1N		Toluene	36	37	*S*

[a] Hexane–Et_2O in the ratio 3 : 2. [b] Determined by HPLC, Chiralcel OD–H. [c] Isolated yields. [d] Established through optical rotation.

By using optically active (*R*)-1-phenylethan-1-ol as a catalyst, instead of the BODOLs, only racemic 1-phenylpropan-1-ol was obtained in 12% yield (GC). As no optical activity could be detected, this indicated that the background reaction was slightly enhanced by the addition of alcohols, but that no autocatalysis occurred.

When using the 2-picolyl-BODOL§ **16** the enantioselectivity was reversed but a fair yield and good ee of (*S*)-1-phenylpropan-1-ol was obtained (entry 1E). Changing the solvent to toluene in this case gave a lower yield, but the ee was almost the same (entry 1F). Similar reversals of enantioselectivity have been observed when using fenchone-based catalysts.[20]

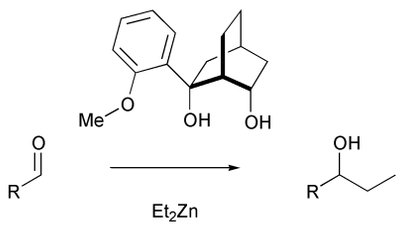
When applying a catalyst having a methyl group at the bridgehead position between the hydroxy groups as in **17** both yield and ee were lower than with **14** (entry 1G). This may be explained by the bulk of the methyl group interfering with the structure of the catalyst. It should also be noted that the bridgehead methyl in **17** caused a reversal of the enantioselectivity in comparison with **14**. A change of solvent to toluene made a considerable improvement in the ee of **17** (from 28 to 46% ee) and had a positive effect on the yield as well (entry 1H). On the other hand, when the methyl group was positioned at the back side bridgehead (position 4), as in **18**, the differences in yield and ee compared to those achieved with **14** were negligible (entry 1I). In this case both the yield and ee of (*R*)-1-phenylpropan-1-ol decreased substantially when the reaction was performed in toluene (entry 1J).

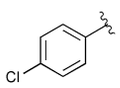
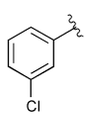
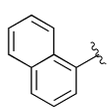
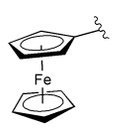
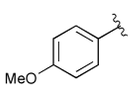
The less rigid diols **19** and **20** worked as catalysts but gave inferior results. Interestingly, **19**, with the hydroxy groups *syn*-oriented, was better than **20** (entries 1K–1N). More interesting was the observation that **19** worked better than **17** as a catalyst. Thus, in forming a zinc complex, **17** is apparently forced to place its bridgehead methyl group unfavourably, while **19**, due to its greater flexibility may compensate for this to some degree, by adjusting the cyclohexane ring conformation.

It should also be mentioned that the catalysts could be isolated after the reaction in good yields (>80%). The recycled catalysts could be used without any significant changes in either yield or ee.

§ The IUPAC name for picolyl is methylpyridyl.

Table 2 Addition of diethylzinc to aromatic aldehydes using anisyl-BODOL



Entry	R	Ee[a] (%)	Yield[b] (%)	Config.[d]
2A		92	86	*R*
2B		92	88	*R*
2C		88	80	*R*
2D		79[c]	82	*R*
2E		<5[e]	54	*R*
2F		–	72[f]	*R*
2G		65	74	*R*

[a] Determined by HPLC, Chiralcel OD–H. [b] Isolated yields. [c] Determined by GC, Supelco β-DEX. [d] Established through optical rotation. [e] Determined by optical rotation. [f] Isolated after 24 h at 22 °C.

The catalytic addition to some other aromatic aldehydes

As anisyl-BODOL appeared to be the best catalyst it was used in the addition of diethylzinc to some aromatic aldehydes other than benzaldehyde. The results, using diethyl ether–hexane as the solvent under the standard conditions (0 °C, 40 h) are shown in Table 2. No significant changes in the ee were observed when the electron withdrawing Cl-substituents were located in either the 4- or 3-positions of the benzaldehyde (entries 2A and 2B). With the sterically more challenging naphthalene-1-carbaldehyde a somewhat lower ee was obtained (entry 2C) and thiophene-2-carbaldehyde gave a still lower ee (entry 2D). In all four cases the yields were quite high.

In the thiophene case some 2-thienylmethanol could also be isolated (10%). It is not unusual to observe a reduction of the aldehyde to the corresponding primary alcohol when the diethylzinc addition becomes slower.[21] This was also noticed for a few of the other catalysts (**15**, **17**, **19** and **20**).

The use of pyridine-2-carbaldehyde gave a very rapid addition, which was complete within a few minutes (entry 2E). However, the ee in this reaction was very small and was not analysed in further detail. Soai's group has reported autocatalysis with several nitrogen-containing hetero-aromatic aldehydes, but does not mention pyridine-2-carbaldehyde.[22,23] Other authors have also observed that the addition of zinc reagents to this aldehyde may result in low ees.[24–26] It is believed that the presence of the coordinating nitrogen close to the aldehyde group, allows the formation of a bidentate complex of pyridine-2-carbaldehyde, thereby accelerating the non-catalysed reaction.[26] In the reaction with ferrocene carbaldehyde no product could be isolated when performing the reaction under the standard conditions. Increasing the temperature to 22 °C for 24 h produced racemic 1-ferrocenylpropan-1-ol in 72% yield (entry 2F). As expected, having an electron donating methoxy-group in the 4-position gave a lower ee and yield in comparison with benzaldehyde (entry 2G).

Investigation of non-linear effects

Not long after the first observation of a NLE (Non Linear Effect) was reported in asymmetric catalysis,[27] a strong asymmetric amplification in the catalytic asymmetric diethylzinc addition to aldehydes was found.[28,29] Therefore, the catalytic asymmetric organozinc additions to carbonyl compounds, with amino alcohols as catalysts, are closely associated with NLEs. However, to our knowledge, only two such investigations have been performed with diols as catalysts in the addition of diethylzinc to aldehydes. These investigations were performed with the catalysts **12b** and **6**. A positive NLE was found when using the latter, but no obvious NLE was noticed with **12b**.[15] As a NLE requires that either the catalyst itself or a precatalyst (in equilibrium with the true catalyst) must incorporate at least two ligands, it seems likely that the bulk of **12b** may prevent formation of dimers or larger complexes.

We have previously observed dimer formation between **14** and $Ti(OPr^i)_4$ in toluene-d_8, benzene-d_6 and THF-d_8 using NMR spectroscopy,[19] a positive NLE was indeed found in the asymmetric reduction of ketones with catecholborane, catalysed by a mixture of **14** and $Ti(OPr^i)_4$. Naturally, we wanted to see if this also was the case with **14** in the asymmetric addition of diethylzinc to benzaldehyde. Unfortunately, structural information of the complex(es) formed between **14** and Et_2Zn in toluene-d_8 could not be acquired by NMR spectroscopy, due to a multitude of low intensity peaks in addition to peak broadening. Allowing the solutions to mature or addition of more Et_2Zn did not improve the spectra. Also, efforts to obtain X-ray quality crystals were unsuccessful. The solid material obtained from mixtures of **14** and Et_2Zn produced only an amorphous material not suitable for X-ray crystallographic analysis.

Indications of the presence of dimeric (or higher) species came from the pronounced positive NLE that was seen when performing the reaction with a varying enantiomeric purity of **14** (Fig. 5). When performing the reactions with 5 mol% of the catalyst having an ee below 30% the ee determinations of (*R*)-1-phenylpropan-1-ol became too uncertain, therefore, 10 mol% of **14** was used throughout the NLE investigation.

Both the ML_n model of Girard and Kagan[30] and the extension of Noyori and co-workers[31] suggest the formation of equilibrium mixtures of heterochiral and homochiral complexes. In the Girard–Kagan model the equilibrium between these complexes, in combination with their different reaction rates as catalysts, led to the observed NLE. For the diethylzinc addition catalysed by amino alcohols, the model proposed by Noyori and co-workers, is similar to the ML_n-model, but a mechanistic extension is introduced, in which the larger complexes are in equilibrium with monomeric species, which then are the active catalysts. Thus, in this model the catalytically incompetent larger complexes (both hetero- and homochiral) can be viewed as storage forms of the monomeric catalyst. The equilibria between these large and monomeric complexes dictate the proportions of the active, monomeric catalysts. More detailed discussions concerning the kinetics and mathematical models involved in autocatalysis and NLE have been published by Blackmond *et al.*[32–36] In our case, no further interpretation of

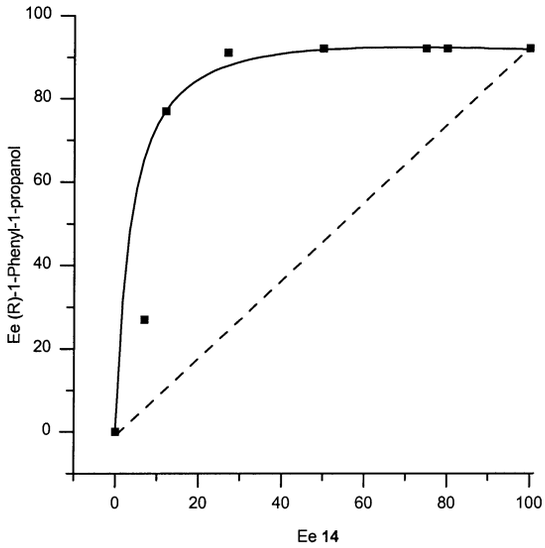
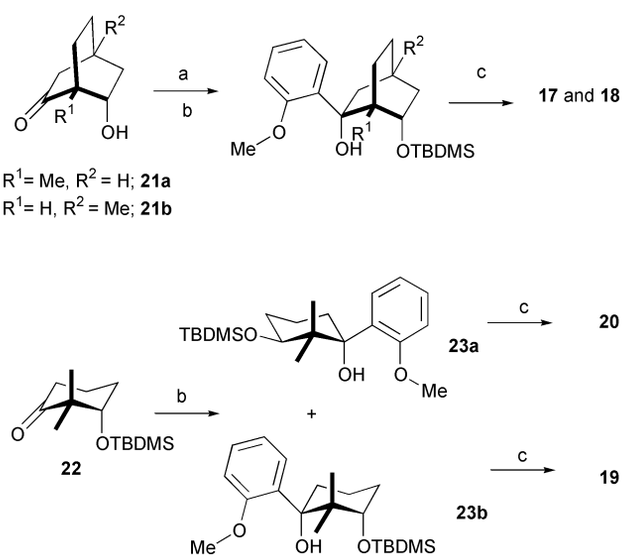


Fig. 5 The positive NLE, using 10% of **14** as a catalyst.

the NLE has been performed other than the obvious notion of dimeric or larger complexes.

As the diols **14**–**20** were synthesised by methods essentially described earlier, only a few comments concerning their synthesis will be made here. The alcohols **21a** and **21b** were synthesized according to literature procedures.[37] After protecting them as TBDMS-ethers, the addition of the anisyllithium–$CeCl_3$ reagent was completely stereoselective.[18,19,38]

Compound **22** was also synthesized according to literature procedures.[39] In contrast to **21a** and **21b**, the addition of the anisyllithium–$CeCl_3$ reagent was not stereoselective when applied on compound **22**. Instead, a 3 : 1 diastereomeric mixture of **23a** and **23b** was isolated (Scheme 1). However,



Scheme 1 a) TBDMSCl, imidazole, DMF. b) Anisyllithium, $CeCl_3$, THF. c) Bu_4NF, THF.

these compounds could easily be separated by column chromatography.

Removal of the TBDMS groups with Bu_4NF then gave the desired compounds **14**–**20** in high yields. It was noticed that the monocyclic diols **19** and **20** were not as prone to acid degradation as the bicyclic compounds **14**–**16**,[19] possibly due to the absence of steric strain. Also **17** was remarkably stable towards acid. If we assume that this degradation proceeds *via* carbocation formation at the benzylic position, the cation stabilisation (by delocalisation of charge into the aromatic ring) would require a planar arrangement of the aromatic ring and the cationic site at C1–$C2^+$–C3. This may be hindered, due to steric interference, between the 1-methyl group and the aromatic substituent.

An unambiguous structure determination of the diastereomers **19** and **20** could not be made by NMR spectroscopy. However, the structures of **20** and **23b** were ascertained by X-ray crystallography, which thereby cleared the structure of **19**. The crystallographic data will be published elsewhere.[40]

Experimental

All reactions were carried out in oven-dried glassware under an argon atmosphere using anhydrous solvents (distilled from CaH_2 and dried over molecular sieves). Compounds **14**, **15** and **16** were synthesised according to our previous procedures.[19] Also compounds **21a**,**b** and **22** were synthesised according to the literature.[37,39] Benzaldehyde was distilled prior to use and the other aldehydes and diethylzinc were used as delivered (Aldrich). TLC was carried out on silica gel (60 F_{254}, Merck) and spots were visualised with UV light and then with a solution of *p*-methoxybenzaldehyde (10 ml), concentrated sulfuric acid (50 ml) and ethanol (95%, 950 ml). Flash column chromatography was performed on Matrex (25–70 μm) silica gel. Melting points were taken on a Sanyo Gallenkamp melting point apparatus (MPD.350.BM3.5) and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter at 22 °C and are given in 10^{-1} deg cm^2 g^{-1}. Elemental analyses of C, H, and N were performed by H. Kolbe Mikroanalytisches Laboratorium. HPLC analyses were performed on a Daicel OD–H column (250 × 4.6 id, 5 μm) and GC analyses were performed on a β-DEX column (Supelco, 30 m × 0.25 mm id, 25 μm film thickness). All NMR data were recorded on a Bruker DRX 400 spectrometer, if not otherwise mentioned, and the chemical shifts were measured using the solvents as internal references {$CHCl_3$ (^{1}H, 7.27 ppm), $CDCl_3$ (^{13}C, 77.23 ppm), C_6H_6 (^{1}H, 7.16 ppm), C_6D_6 (^{13}C, 128.39 ppm)}.

(1*R*,2*R*,4*S*,6*S*)-2-(2-Methoxyphenyl)-1-methylbicyclo[2.2.2]-octane-2,6-diol (17)

Keto-alcohol **21a** (0.45 g, 2.9 mmol) was added to dry DMF (2 ml) followed by imidazole (0.49 g, 7.3 mmol) and TBDMSCl (0.55 g, 3.7 mmol). The mixture was kept overnight at rt, and then diethyl ether (60 ml) and water (40 ml) were added. The organic phase was separated, washed with HCl (25 ml, 0.5 M), aqueous saturated $NaHCO_3$ (25 ml) and brine (25 ml). The organic solution was then dried (Na_2SO_4), filtered and concentrated at reduced pressure. Chromatography (SiO_2, heptane–EtOAc: 90 : 10) of the residue gave (1*R*,4*S*,6*S*)-6-*tert*-butyldimethylsilyloxy-1-methylbicyclo[2.2.2]octane-2-one (0.78 g, quantitatively) as a clear oil, which was used in the next step.

A suspension of $CeCl_3$ (2.0 g, 5.4 mmol) in THF (15 ml) was prepared as previously described.[19] The resulting mixture was stirred for 5 min at 0 °C and then for 5 h at rt. This should result in a "milky suspension" without any large fragments. The suspension was then cooled to −78 °C, followed by addition of anisyllithium (prepared by addition of n-BuLi (3.7 ml, 5.9 mmol) to anisole (0.87 ml, 8.0 mmol) in 6 ml THF at rt) and the resulting yellow mixture was stirred for 1 h at −78 °C. A solution of (1*R*,4*S*,6*S*)-6-*tert*-butyldimethylsilyloxy-1-methylbicyclo[2.2.2]octane-2-one (0.49 g, 1.9 mmol in THF 5 ml) was then added and the mixture was allowed to reach rt overnight. Thereafter aqueous saturated NH_4Cl (25 ml) was added. The phases were separated and the water phase was extracted with ether (2 × 20 ml). The combined organic phase was dried (Na_2SO_4) and filtered through a pad of SiO_2, in order to remove inorganic cerium salts. The solvent was removed under vacuum, and the residue was then diluted with cold, dry THF (30 ml).

Bu_4NF (0.75 g, 2.4 mmol) was added to this solution and the reaction mixture was stirred overnight. TLC analysis confirmed that the deprotection was complete. The reaction mixture was concentrated under reduced pressure to yield an orange oil, which was diluted with 50 ml of EtOAc and the organic solution was washed with brine (3 × 20 ml) and dried (Na_2SO_4). Filtration and removal of the solvent under reduced pressure gave an oil, which was purified by flash chromatography (SiO_2, heptane–EtOAc: 60 : 40, R_f = 0.29) to yield the title compound as crystals (0.37 g, 49% from **21a**). Mp 169 °C, $[a]_D$ +61.9 (*c* 0.512, MeOH). $\delta_H(C_6D_6)$ 0.8 (1H, m), 1.03 (3H, s), 1.2–1.4 (3H, m), 1.77 (1H, m), 1.94 (1H, m), 2.20 (1H, m), 2.31 (1H, m), 2.47 (1H, m), 2.98 (3H, s), 3.68 (1H, m), 4.55 (1H, br d, *J* 11 Hz), 6.3 (1H, br s), 6.40 (1H, dd, *J* 1.1 and 8.2 Hz), 6.82 (1H, m), 6.98 (1H, m), 7.12 (1H, br d). $\delta_C(C_6D_6)$ 19.8, 25.5, 27.2, 29.6, 40.7, 41.2, 45.5, 55.5, 76.4, 83.5, 112.7, 121.4, 128.3, 130.1, 132.8, 158.0 (Found: C, 73.18; H, 8.48. $C_{16}H_{22}O_3$ requires C, 73.25; H, 8.45%).

(1*R*,2*R*,4*S*, 6*S*)-2-(2-Methoxyphenyl)-4-methylbicyclo[2.2.2]-octane-2,6-diol (18)

Following the method mentioned above for the synthesis of **17**, the keto-alcohol **21b**, gave after flash chromatography (SiO_2, pentane–acetone: 80 : 20, R_f = 0.22) the title compound (27% from **21b**) as crystals. Mp 85–87 °C, $[a]_D$ +46.7 (*c* 0.6, MeOH). $\delta_H(C_6D_6)$ 0.90 (3H, s), 1.08–0.90 (2H, m), 1.29–1.08 (2H, m), 1.89 (1H, m), 1.96 (1H, m), 2.05–2.20 (2H, m), 2.66 (1H, m), 3.13 (3H, s), 4.18 (1H, m), 4.47 (1H, s), 4.63 (1H, d, *J* 11.2 Hz), 6.53 (1H, m), 6.87 (1H, m), 7.09 (1H, m), 7.22 (1H, dd, *J* 1.8 and 7.8 Hz). $\delta_C(C_6D_6)$ 22.6, 28.1, 30.6, 31.0, 40.3, 46.5, 50.1, 55.0, 71.7, 79.0, 112.2, 121.2, 126.9, 128.3, 135.0, 158.1 (Found: C, 73.18; H, 8.48. $C_{16}H_{22}O_3$ requires C, 73.25; H, 8.45%).

(1*R*,3*S*)- and (1*S*,3*S*)-1-(2-Methoxyphenyl)-3-*tert*-butyldimethylsiloxy-2,2-dimethylcyclohexanol (23a) and (23b)

A solution of (*S*)-3-*tert*-butyldimethylsilyloxy-2,2-dimethylcyclohexanone (**22**) (1.6 g, 6.0 mmol in THF 5 ml) was added to an anisyllithium–$CeCl_3$ reagent prepared as mentioned {from $CeCl_3$ (3.6 g, 9.8 mmol), THF (25 ml) anisole (1 ml, 9 mmol) and Bu–Li (6.6 ml 11 mmol in hexane)}. The mixture was allowed to reach rt overnight, thereafter aqueous saturated NH_4Cl (20 ml) was added and the phases were separated and the water phase was extracted with diethyl ether (3 × 20 ml). The combined organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography (SiO_2, CH_2Cl_2) of the residue gave the title compounds **23a** (R_f = 0.67, 1.45 g, 66.5%) and **23b** (R_f = 0.54, 0.46 g, 21%) as crystals.

23a. Mp: 81 °C, $[a]_D$ +42 (*c* 0.95 in $CHCl_3$). $\delta_H(CDCl_3)$ 0.08 (6H, s), 0.75 (3H, s), 0.88 (3H, s), 0.91 (9H, s), 1.60 (4H, m), 1.95 (1H, m), 2.40 (1H, m), 3.89 (3H, s), 4.05 (1H, dd, *J* 11.1 and 4.7 Hz), 5.85 (1H, br s), 6.96 (2H, m), 7.25 (2H, m). δ_C(Bruker ARX 300, $CDCl_3$) −4.6, −3.7, 17.2, 18.3, 19.4, 21.9, 26.1, 31.2, 34.2, 45.6, 55.9, 74.2, 82.0, 112.3, 120.8, 128.2, 129.9, 132.0, 157.9 [Found (HRMS, CI, CH_4): M^+, 363.2348. $C_{21}H_{35}O_3Si$ requires *M*, 363.2355].

23b. Mp 88–89 °C, $[a]_D$ +51.9 (*c* 1.08 in $CHCl_3$). $\delta_H(CDCl_3)$ 0.13 (6H, s), 0.89 (3H, s), 0.91 (3H, s), 0.98 (9H, s), 1.60 (4H, m), 2.05 (2H, m), 3.30 (1H, m), 3.77 (3H, s), 5.7 (1H, br s), 6.88 (2H, dd, *J* 8.16 and 1.11 Hz), 6.96 (1H, m), 7.21 (1H, m), 7.94 (1H, dd, *J* 7.95 and 1.84 Hz). δ_C(Bruker ARX 300, $CDCl_3$) −4.9, −4.4, 16.2, 18.2, 22.9, 24.9, 26.0, 29.4, 33.1, 42.2, 55.5, 79.6, 80.5, 112.2, 120.3, 128.0, 131.9, 133.0, 157.3 [Found (HRMS, CI, CH_4): M^+, 365.2359. $C_{21}H_{35}O_3Si$ requires *M*, 363.2355].

(1*S*,3*S*)-1-(2-Methoxyphenyl)-2,2-dimethylcyclohexane-1,3-diol (19)

Compound **23b** (0.41 g, 1.1 mmol) was dissolved in THF (30 ml). Bu_4NF (0.43 g, 1.4 mmol) was added and the reaction mixture was stirred overnight. TLC analysis confirmed that the deprotection was complete. The reaction mixture was concentrated under reduced pressure to yield an orange oil, which was diluted with 50 ml of EtOAc and the organic solution was washed with brine (3 × 20 ml) and dried (Na_2SO_4). Filtration and removal of the solvent under reduced pressure gave an oil, which was purified by flash chromatography (SiO_2, 10% Et_2O in CH_2Cl_2) to yield the title compound as crystals (0.28 g, 97%). Mp 77–78 °C, $[a]_D$ −19.8 (*c* 1.26 in $CHCl_3$). $\delta_H(CDCl_3)$ 0.8 (3H, s), 1.06 (3H, s), 1.58 (1H, m), 1.76 (2H, m), 1.91 (1H, m), 2.20 (1H, m), 2.50 (1H, m), 3.52 (1H, m), 3.91 (3H, s), 6.5 (1H, br s), 6.94–7.05 (2H, m), 7.17 (1H, br d, 7.1 Hz), 7.29–7.24 (1H, m). $\delta_C(CDCl_3)$ 15.9, 22.8, 24.8, 29.3, 34.4, 42.2, 56.0, 78.7, 83.0, 112.3, 121.2, 128.6, 129.4, 131.2, 157.7 (Found: C, 71.83; H, 8.92. $C_{15}H_{22}O_3$ requires C, 71.97; H, 8.86%).

(1*R*,3*S*)-1-(2-Methoxyphenyl)-2,2-dimethylcyclohexane-1,3-diol (20)

Following the method for the synthesis of **19**, using **23a**, with the exception that the reaction mixture had to be refluxed to remove the protecting group, gave the title compound (97%) as crystals. Mp 119 °C, $[a]_D$ +58.1 (*c* 1.26 in $CHCl_3$). $\delta_H(CDCl_3)$ 0.75 (3H, s), 1.08 (3H, s), 1.97–1.53 (4H, m), 2.20 (2H, m), 2.50 (1H, br s), 3.51 (1H, dd, *J* 14.0 and 7.02 Hz), 3.91 (3H, s), 4.89 (1H, br s), 6.97 (2H, m), 7.26 (2H, m). $\delta_C(CDCl_3)$ 17.0, 19.7, 21.5, 31.0, 34.4, 45.4, 56.2, 74.1, 82.0, 112.6, 121.1, 128.6, 130.2, 132.0, 158.2 (Found: C, 72.05; H, 8.78. $C_{15}H_{22}O_3$ requires C, 71.97; H, 8.86%).

Addition of Et_2Zn to aldehydes (general procedure)

Under an argon atmosphere the catalyst (50 μmol) was dissolved in diethyl ether (2.0 ml) and cooled to 0 °C. Thereafter diethylzinc (3.0 ml, 1.0 M in hexanes, 3.0 mmol) was added and the mixture was allowed to stir at 0 °C for 15 min whereafter the aldehyde (1 mmol, neat) was added. After stirring the mixture at 0 °C for 40 h the reaction was quenched by the addition of saturated NH_4Cl (7 ml) at 0 °C. Stirring at this temperature was continued for a few minutes before water (25 ml) was added. The organic phase was separated and the aqueous phase was extracted with EtOAc (2 × 25 ml). The combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography of the residue then gave the desired product. The chemical structures were established by ^1H NMR spectroscopy and the enantiomeric excesses were determined by enantioselective HPLC-, GC-chromatography or by specific rotation (see below).

Determination of ee by HPLC

HPLC: Chiralcel OD–H (Daicel) 250 × 4.6 mm, rt, flow rate: 0.5 ml min^{-1}, detection at 245 nm. Anisyl-BODOL (**14**). Solvent, hexane–Pr^{i}OH: 80 : 20, 13 min (1*S*,2*S*,4*R*,6*R*), 17 min (1*R*,2*R*,4*S*,6*S*).

1-Phenylpropan-1-ol, $[a]_D$ +43 (*c* in 3.2, $CHCl_3$), {lit.[41] (*S*) $[a]_D$ −48.5 (*c* 4 in $CHCl_3$)}. Solvent, hexane–Pr^{i}OH: 97.5 : 2.5, (*R*) 25.4 min, (*S*) 27.1 min.

1-(4-Chlorophenyl)propan-1-ol, $[a]_D$ +27 (*c* 3.8 in C_6H_6) {lit.[41] (*S*) $[a]_D$ −28.2 (*c* 5.01 in C_6H_6)}. Solvent, hexane–Pr^{i}OH: 95 : 5, (*S*) 14.8 min, (*R*) 15.4 min.

1-(3-Chlorophenyl)propan-1-ol, $[a]_D$ +28.0 (*c* 2.23 in C_6H_6) {lit.[42] (*R*) $[a]_D$ +24.2, toluene}. Solvent, hexane–Pr^{i}OH: 95 : 5 (*S*) 14.7 min, (*R*) 15.4 min.

1-Naphthylpropan-1-ol, $[a]_D$ +45.8 (*c* 2.51 in $CHCl_3$) {lit.[43] (*R*) $[a]_D$ +55.6, $CHCl_3$}. Solvent, hexane–Pr^{i}OH: 90 : 10, (*S*) 15.8 min, (*R*) 26.8 min.

1-(4-Methoxyphenyl)propan-1-ol, $[\alpha]_D$ +17.6 (*c* 2.8 in C_6H_6), {lit.[16] $[\alpha]_D$ +31.8 (*c* 3.5 in C_6H_6)}. Solvent, hexane–Pr^{i}OH: 95 : 5, (*R*) 20.4 min, (*S*) 23.7 min.

Determination of ee by GC

Column: β-DEX (Supelco) 30 m × 0.25 mm id, 25 μ film thickness.

1-Thiophenepropan-1-ol, $[\alpha]_D$ +19 (*c* 2.1 in $CHCl_3$) {lit.[44] (*R*) $[\alpha]_D$ +25.9 (*c* 2.1 in $CHCl_3$)} GC: isothermal 110 °C, 30 min (*R*) 15.4 min (*S*) 16.1 min.

Determination of ee by optical rotation

Since baseline separation could not be achieved for the compounds below and the ees were low the enantiomeric purity was determined by optical rotation with a Perkin-Elmer 241 polarimeter at 22 °C.

1-(Pyridin-2-yl)propan-1-ol, $[\alpha]_D$ +5.2 (*c* 2.1 in $CHCl_3$) {lit.[25] (*R*) $[\alpha]_D$ +5.7, (*c* 2.25 in $CHCl_3$, (5.4% ee))}.

1-Ferrocenylpropan-1-ol, $[\alpha]_D$ −0.1 (*c* 1.7 in C_6H_6) {lit.[45](*S*) $[\alpha]_D$ +56, (*c* 1.4 in C_6H_6)}.

Acknowledgements

We thank The Swedish Research Council and the Royal Physiographic Society in Lund for economic support.

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