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Bicyclo[2.2.2]octane-derived chiral ligands—synthesis and application of BODOLs in the asymmetric reduction of acetophenone with catecholborane

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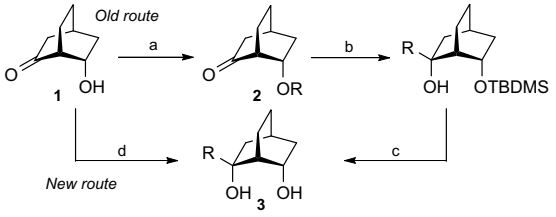
ABSTRACT

An improved synthetic route to the bicyclo[2.2.2]octane-2,6-diol ligands (2,6-BODOLs) allowed an increased structural variation of the ligand side-arm. The addition of aromatic or vinylic Grignard reagents to hydroxyketone **1** was highly selective and ligands **3f**–**3l** were isolated in 84–97% yield. The addition of alkyl Grignard reagents containing β-hydrogens resulted in lower yields (13–71%) due to competing ketone reduction. A number of 2,5-BODOLs were synthesized using a similar methodology. The ligands, together with $Ti(OiPr)_4$, were tested in the asymmetric reduction of acetophenone with catecholborane (up to 98% ee). 1-Naphthyl-BODOL **3i** was employed as an allylboration reagent to benzaldehyde together with $Sc(OTf)_3$, resulting in (1*S*)-1-phenyl-3-buten-1-ol in 80% ee.

1. Introduction

Bicyclo[2.2.2]octane-based compounds are valuable rigid building blocks in natural product synthesis[1,2] and some derivatives have been investigated as therapeutic agents for cocaine abuse,[3] antimalarial drugs[4] as well as utilized as chiral ligands.[5–10] A number of Ti-diolates, and other complexes, useful as catalysts for the enantioselective reduction of ketones have been reported in the literature.[11–16] Most of these complexes were based on structures such as BINOLs[17] and TADDOLs,[18] which have often served as lead structures for the development of improved catalysts. The design of novel ligand motifs is one of the major research objectives in the search for new and more efficient chiral catalysts, and catalysts with complementary features to those already developed. Not many 1,3-diols have been demonstrated to function as efficient ligands in metal-induced asymmetric catalysis. Amongst those reported are the aluminium complexes of the menthone and isomenthone-derived 1,3-diols, which were successfully applied to the asymmetric Diels–Alder reaction of 3-crotonoyl-2-oxazolidinone and cyclopentadiene[19] and to the Mukaiyama aldol reaction of the TMS enol ether of methyl isobutyrate and isobutyraldehyde,[20] respectively. Several bicyclo[2.2.2]octane-diol (BODOL) ligands have been reported to work as efficient asymmetric catalysts in the titanium catalyzed catecholborane (CBH) reduction of ketones[21–23] and in the diethylzinc addition to aromatic aldehydes.[24] In previous work, the ligands were synthesized by a multi-step procedure involving a bulky silyl protecting group for control of the stereoselectivity ('old route', Scheme 1). The structural variation of the side arm at the 2-position of the BODOLs was limited to those groups that could be introduced via lithium organics obtained by direct lithiation.[22] Naturally, it was desirable to include BODOLs having many types of side groups as well as derivatives with structural modifications of the bicyclic framework. Moreover, for large scale preparation of the ligands, we found this synthetic route unsatisfactory in terms of yields. Herein, we report a direct and highly selective synthesis of an extended number of BODOLs ('new route', Scheme 1) and related analogues, as well as their function as ligands in the titanium-catalyzed CBH reduction of ketones.



Scheme 1. Reagents and conditions: (a) TBDMSCl, DMF, imidazole; (b) RLi, $CeCl_3$, THF, −78 °C→rt; (c) Bu_4NF, THF; (d) RMgX, ether/THF or RLi, ether.

2. Results and discussion

In the new protocol, BODOLs **3a**–**l** were synthesized by the addition of the corresponding Grignard reagent to hydroxyketone **1**[25–27] in ether solution without prior protection (Table 1). The reaction was performed at 25 °C using the organomagnesium

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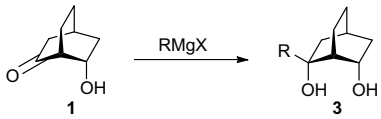
Table 1
Reaction of hydroxy ketone **1** with Grignard reagents (at 25 °C for 1 h) in ether/THF



1 **3**

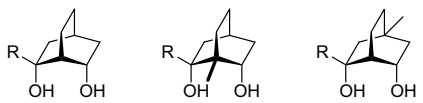
Entry	RMgBr (R=)	Product[f]	Yield (%)[a]
1	Me[b]	**3a**	99
2	Et[c]	**3b** (71:29)	71
3	Bu[d]	**3c** (55:45)	33
4	*i*Pr[d]	**3d** (13:87)	13
5	c-Hex[d]	**3e** (29:71)	20
6	Vinyl[c]	**3f**	88
7	Ph[c]	**3g**	94
8	4-Biphenyl[e]	**3h**	88
9	1-Naphthyl[d]	**3i**	84
10	2-Naphthyl[e]	**3j**	84
11	2-Methylphenyl[d]	**3k**	97
12	2-Ethylphenyl[d]	**3l**	89

[a] Isolated yields.
[b] Commercial reagent, 3.0 M in ether.
[c] Commercial reagent, 1.0 M in THF.
[d] Freshly prepared, 1 M in THF.
[e] Commercial reagent, 0.5 M in THF.
[f] Figures within parentheses correspond to the ratio (determined by GC) of the addition product and the reduction product *endo,endo*-bicyclo[2.2.2]octan-2,6-diol.

bromides in THF of different concentrations, depending on the commercial solutions.

In the synthesis of the substituted BODOLs, 1 equiv of the reagent was added upon which a precipitate was formed, which dissolved after the addition of another 1.5 equiv. Substances **3c–e**, **3i** and **3k–l** were synthesized using freshly prepared Grignard reagents in THF with an approximate concentration of 1 M. GC analysis of the product mixtures showed high selectivity in all cases (>96% de), favouring the desired products (*endo*-diols). Addition of the vinylic and aromatic Grignard reagents resulted in high yields (entries 6–12). However, a large variation was observed with the alkyl Grignard reagents (entries 1–5). The lower yields obtained when using Grignard reagents containing β-hydrogens (entries 2–5) were caused by competing reduction of the carbonyl group. The reduction resulted in almost exclusive formation of *endo,endo*-bicyclo[2.2.2]octan-2,6-diol. No significant difference in yield or selectivity was observed when the corresponding organomagnesium chlorides were used.

In order to easily obtain BODOLs with a large structural variation of the substituent at the 2-position, the direct addition of organolithium reagents to **1** was investigated. The addition of PhLi (2 h at −78 °C in ether) was tested and it afforded **3f** in good yield (79%). However, changing the solvent to THF resulted in a lower yield (64%). Moreover, anisyl-BODOLs **4a–c** (Fig. 1) were synthesized by the addition of *o*-anisyllithium to their corresponding hydroxyketone precursors. The isolated yield obtained for **4a** was lower than the yields obtained for **4b** and **4c**. Since full conversion of the starting materials was observed, the difference in yields may be due to loss of material by sublimation at reduced pressure during the work-up procedure.



4a (65%) **4b** (82%) **4c** (75%)

R = o-Anisyl

Figure 1.

The diastereoselectivity for the addition of the lithium reagents was comparable (>96% de) to the results obtained with the Grignard reagents. In those cases where the addition of Grignard reagents containing β-hydrogens resulted in low yields of the desired products, the use of alkyl lithium reagents could be an alternative. Thus, in contrast to the use of BuMgBr as reagent, which resulted in 33% yield of **3c** (entry 3), addition of butyllithium to **1** in ether resulted in 69% yield.

The configuration of **3f** and **3g** was confirmed by NOESY correlations between the vinylic/aromatic protons of the ligand side arm and the methylene protons in the non-substituted ethylene bridge of the bicyclic structures. Moreover, samples of anisyl-BODOL **4a** (Fig. 1) synthesized by both routes (Scheme 1) were found to be identical.

The stereochemical outcome in the nucleophilic additions to hydroxy carbonyl compounds can often be predicted by the Cram chelation model. Using the pBP/DN* model,[28] DFT calculations of the hydroxy MgBr salt, formed by the addition of 1 equiv of the Grignard reagent to **1**, indicated that a six-membered chelate could be formed (Fig. 2).

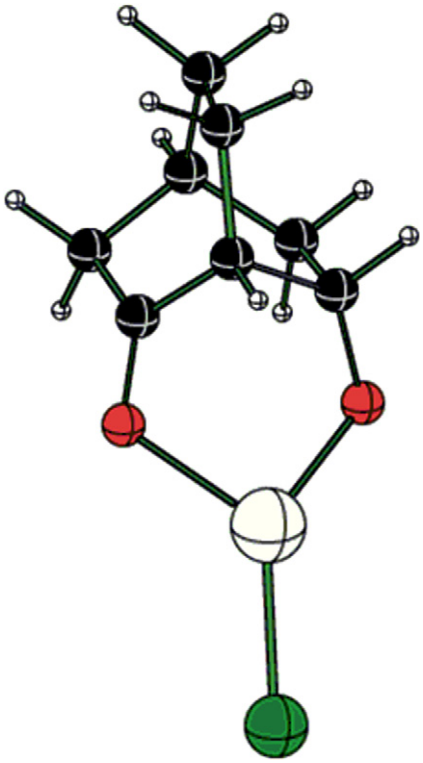


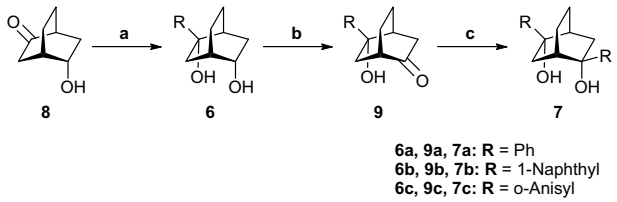
Figure 2.

The formation of a chelated intermediate would explain not only explain the reactivity but also the high selectivity observed upon the addition of the second equivalent of the reagent, which would then be delivered from the less-hindered face of the carbonyl. It should be noted that the addition of Grignard and lithium reagents to the TBDMS-protected hydroxyketone **2** did not occur at all without the aid of $CeCl_3$ and previous attempts to synthesize the ligand **3i** by the addition of 1-naphthyllithium/$CeCl_3$ to **2** (Scheme 1) failed, resulting in recovered starting material. The improved synthetic route thus opened the possibility for easy modification and synthesis of a wide range of new BODOLs.

Further development of the bicyclo[2.2.2]octane-based ligand system was achieved by the synthesis of a number of 2,5-BODOLs **6** (Fig. 3) and their corresponding C_2-symmetric counterparts **7**.

The synthesis of BODOLs with substituents at the 2,5-position (**6a–c**, Scheme 2) was performed as for **3**, using the hydroxy ketone **8**[29] as starting material.

Figure 3.



Scheme 2. Reagents and conditions: (a) RMgBr, ether/THF, rt or *o*-anisyllithium, THF, rt; (b) TPAP, NMO, 4 Å MS, DCM, rt; (c) RMgBr, ether/THF, rt or *o*-anisyllithium, THF, rt.

The addition of Grignard reagents to **8** was sluggish and it resulted in low yields. As an example, the addition of 2.5 equiv of PhMgBr resulted in a 22% yield of **6a**. Nevertheless, the diastereoselectivity was high (>94% de) and the yields were improved by a 'cyclic procedure' involving restoration of the ketone from the enolate by the addition of an equimolar amount of water followed by the addition of another portion of the organometallic reagent, repeatedly three times (Table 2). The addition of an excess of *o*-anisyllithium reagent to **8** (entry 3) resulted in an acceptable yield of **6c** (77%), without the use of the cyclic procedure.

Table 2
Addition of Grignard reagents or *o*-anisyllithium hydroxy ketones **8** and **9**

Entry	Substrate	Reagent	Product	Yield[d] (%)
1	**8**	PhMgBr[a]	**6a**	54(22)[e]
2	**8**	1-NaphthylMgBr[b]	**6b**	40(29)[e]
3	**8**	*o*-Anisyllithium[c]	**6c**	77[f]
4	**9**	PhMgBr[a]	**7a**	71[e]
5	**9**	1-NaphthylMgBr[b]	**7b**	94[e]
6	**9**	*o*-Anisyllithium[c]	**7c**	63[f]

[a] Commercial reagent, 1 M in THF.
[b] Freshly prepared, 1 M in THF.
[c] Freshly prepared.
[d] Isolated yields.
[e] Yields given were obtained by repeated reagent additions (2.5 equiv) with the quenching of the reaction mixture with equimolar amounts of water between the additions, three times. Figures within parentheses correspond to the yields obtained by the addition of 2.5 equiv of the reagent in one portion.
[f] 4 equiv of the reagent were used.

Oxidation of **6a–c** using tetrapropylammoniumperruthenate (TPAP)[30] afforded the hydroxy ketones **9a–c** in 94% (**9a**), 92% (**9b**) and 97% (**9c**) yield. The C_2-symmetric ligands **7a–c** were obtained by the addition of the second substituent following the same methodology as described for the synthesis of **6a–c**. The addition reactions of **9a–c** to give **7a–c** resulted in somewhat higher yields (entries 4–6), as compared to the addition of the organometallic reagents to **8** (entries 1–3).

Since the introduction of an olefinic bond in the bridge might be useful for future ligand development (anchoring on solid support and fine tuning of the ligand system), ligands **10a–c** (Fig. 4) were synthesized.

Initially, the synthesis of these ligands was attempted, following the same methodology as described for the addition of organometallic reagents to **8**.

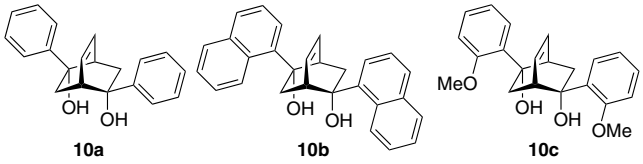
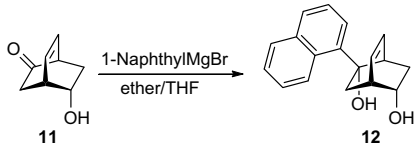


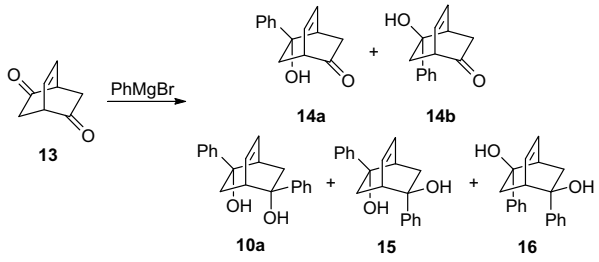
Figure 4.

However, the addition of Grignard reagents to the hydroxy ketone **11**[29] resulted in low yields, despite the use of repeated reagent–water additions as described for hydroxy ketone **8**. While the addition of 1-naphthylMgBr to hydroxy ketone **8** resulted in 40% yield of **6b** (Table 2, entry 2), the analogous addition to hydroxy ketone **11** resulted in only 14% yield of **12** (Scheme 3).



Scheme 3.

Thus, we decided to investigate if the direct addition of the organometallic reagents to the optically active diketone **13**[29,31] (Scheme 4) would be a feasible route to the ligands **10a–c**. Based on the results obtained for the addition reactions to the hydroxy ketones **9a–c**, we reasoned that the diastereoselectivity of the addition of the second substituent was likely to be high. Therefore, the selectivity of the addition of the first substituent to the racemic diketone **13** was investigated by the addition of 1 equiv (or less) of the reagent (Table 3). Whereas the anisyl and 1-naphthyl derivatives decomposed on the GC column, the phenyl derivatives **14a–b**, **10a** and **15–16** (Scheme 4) proved to be stable and were thus used to monitor the addition reactions by GC.



Scheme 4.

As shown in Table 3, the yields were generally low but the better yields were obtained using diethyl ether or *t*BuOMe as bulk solvents. We believe that one major reason of the low yields was the formation of the enolate of **13**, which would prevent further reactions. This was also indicated by the fact that the only other compound in the GC-samples was the starting material **13**. In an attempt to isolate **14a** in a useful yield and with the simplest purification possible, the reaction was performed in hexane with repeated additions of PhMgCl by using the 'cyclic procedure' mentioned. After four reagent additions, the starting material **13** was no longer detected by TLC. This resulted in isolated yields of 32% for **14a**, 18% for **14b**, 6% for **10a**, 23% for **15** and 16% for **16**. Although an acceptable yield of **14a** was obtained, further attempts to reach full conversion of **14a** to obtain **10a** failed in this reaction medium. Whereas the isomer **14b** was consumed to form the diols **15** and **16**, the diol **10a** was formed only in small amounts leaving most of **14a** 'unconverted', possibly due to enolate formation.

Table 3
Addition of 1 equiv of PhMgBr to diketone (±)-**13**[a]

Entry	Solvent	Ratio **14a**:**14b**[b]	Yield of **14a**[c] (%)	Yield of **14b**[c] (%)	Total yield of diols **10a**, **15** and **16**[c] (%)
1	Diethyl ether	30:70 (36:64)	14	33	1.3
2	THF	16:84 (28:82)	2	8	—
3	*t*BuOMe	29:71 (31:69)	13	31	1.5
4	Hexane	54:46 (47:53)	8	7	1.7
5	Hexane/THF	27:73 (39:61)	7	20	0.6
6	Hexane/diethyl ether	41:59 (38:62)	13	18	1.6

[a] The reactions were performed by the addition of PhMgBr (1 M in THF) to 10 mg of **13**/mL solvent at rt under an argon atmosphere.
[b] Figures within parentheses correspond to the addition of 0.2 equiv of PhMgBr.
[c] GC yield. Stearylalcohol was used as an internal standard.

As expected, the selectivity for the addition of the second phenyl group was high and a 95:5 ratio of **10a**:**15** in 20% yield (GC yield) was obtained using ether as the bulk solvent. In THF, **10a** was obtained in less than 1% yield.

PhMgBr and PhMgCl gave similar results, while the addition of PhLi resulted in even lower yields and several unidentified by-products. The use of PhLi together with $CeCl_3$ in THF or ether did not improve the outcome of the reaction.

In a preparative scale experiment using 1 equiv of PhLi/$CeCl_3$ in THF, only 32% of the isolated material consisted of any of the addition products **14a**–**b**, **10a**, **15** or **16**.

A pure fraction of the major by-product was analyzed and found to be the dimeric self-condensation product of the diketone **13**, as verified by mass spectroscopy and ^{1}H NMR. GC-analysis of this compound resulted in decomposition, a peak corresponding to diketone **13** was the only product observed in the chromatogram. The formation of condensation products indicates that enolate formation is most likely the major cause for the low yields obtained in the addition of the organometallic reagents to **13**. Although the selectivity for the addition of the first phenyl group to **13** could be influenced to some extent by the choice of solvent, it was difficult to reach acceptable yields of the diol **10a** in solvents other than ether or *t*BuOMe. Eventually, diols **10a**–**c** were isolated in low yields (23% for **10a** and 12% for **10b** and **10c**) by adding 2 equiv of the corresponding PhMgBr, 1-naphthylMgBr or the *o*-anisyllithium reagent, respectively, to the optically active diketone **13** in ether using the cyclic procedure. In contrast to the Grignard reagents, the yield for **10c** was slightly improved upon by using the *o*-anisyllithium reagent in combination with $CeCl_3$/THF (19%).

The selectivity in the addition of organometallic reagents to 2,5-substituted hydroxy ketones such as **8**, **9** and **14a** was high, but could not be explained by the formation of a cyclic chelate such as that shown for the 2,6-hydroxy ketone **1** (Fig. 2). DFT calculations, using the pBP/DN* model,[28] of the alkoxy MgBr salt of **8** indicated that due to the constrained conformation of the bicyclic core coordination of the Mg to the carbonyl would not be feasible (Fig. 5).

Two low-energy conformations were found, where **8a** was favoured over **8b** with 8.5 kcal/mol. The small relative stabilization observed for **8a**, as compared to **8b**, when the Mg is directed towards the carbonyl functionality is most likely of electrostatic nature. However, upon the addition of the reagent from the sterically more accessible face of the carbonyl, a stabilizing effect of an alkoxy coordinated Mg in a late, or 'product like', transition state is plausible.

The lower yields generally obtained in the additions of the organometallic reagents to the 2,5-hydroxy ketones compared to the 2,6-hydroxy ketone **1**, were most likely caused by competing enolate formation and we speculated that this effect may be enhanced by the alkoxide MgBr salt, contributing to the formation of an enolate. DFT calculations, using the pBP/DN* model,[28] of the alkoxy MgBr salt of the enolate of **8** indicated that enolate formation

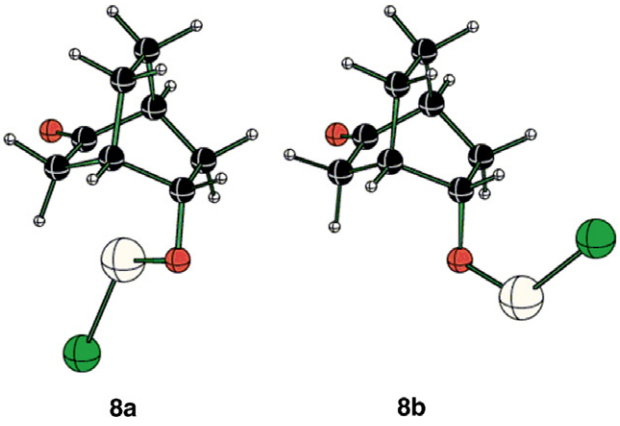


Figure 5.

may be facilitated by the magnesium atom of the intermediate salt having a stabilizing effect on the negative charge developed on the carbonyl α-carbon (Fig. 6).

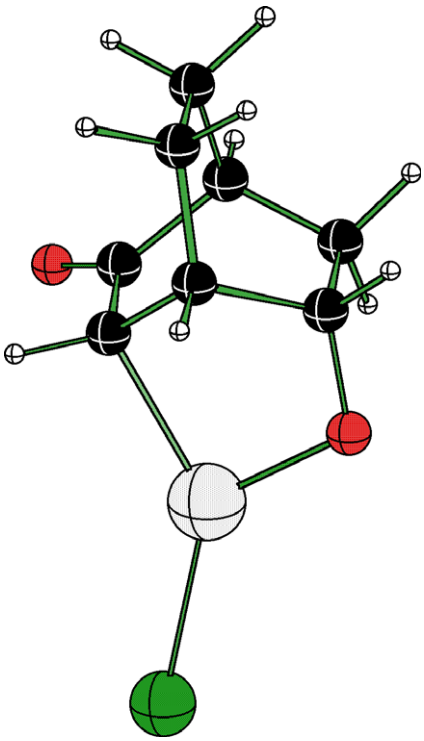


Figure 6.

Since the yields were considerably lower for the hydroxy ketones **11** and **14a** compared to **8** and **9**, enolate formation may be more pronounced for these substrates. Enolate formation facilitated by Mg coordination may also explain the difference in reactivity observed for **14a** and **14b**. This type of enolate stabilization would not be possible for **14b** (Fig. 7).

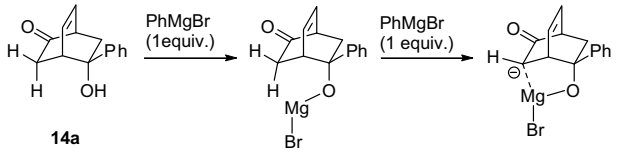


Figure 7.

The configuration of diol **10a** was established by X-ray analysis. Recrystallization from toluene gave colourless prisms suitable for X-ray diffraction. A perspective view of the molecular structure of one of the asymmetric units is given in Figure 8.

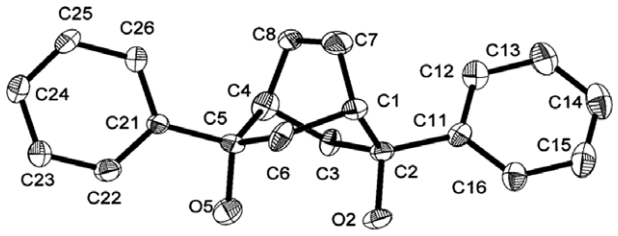


Figure 8. DIAMOND[32] drawing with atomic numbering of one asymmetric unit of **10a**. Hydrogen atoms are omitted for clarity. The ellipsoids denote 30% probability. Selected bond distance (Å) with estimated standard deviation is O2–O5 = 2.84(4).

The configuration of the mono addition product **14a** was in turn established by the observed NOESY correlation between the olefinic protons and aromatic protons of the phenyl group. The addition of PhMgBr to **14a** resulted predominantly in the formation of diol **10a**, providing further evidence for the geometry of **14a** to be correctly assigned. The structure of ligands **10b** and **10c** were confirmed by NOESY correlations between the olefinic bonds and the aromatic side arms. The orientation of the phenyl groups of the saturated analogues **9a** and **7a** was revealed by the catalytic hydrogenation of the olefinic bonds of **14a** and diol **10a**.

The ligands together with Ti(O*i*Pr)$_4$ were screened as catalysts in the asymmetric reduction of acetophenone with catecholborane (CBH). Anisyl-BODOL **4a** (Fig. 2) and phenyl-BODOL **3g** have previously been used as ligands in this reaction with good results (96% and 89% ee, respectively), and were now included in the screening for comparison. The results of the CBH reductions of acetophenone are presented in Table 4.

Amongst the BODOLs with aliphatic sidearms (entries 1A–E), ligand **3a**, possessing the least sterically demanding substituent gave the best result. Both an increased length (entries 1A–C) and increased bulkiness (entries 1D and E) of the aliphatic side chain resulted in lower yields and ee's. The best performing ligands ($\geqslant$94% ee) were those with an aromatic side arm with a substituent in the aromatic *ortho*-position (entries 1I, 1K–M and 1O), all giving considerably higher ee's as compared to the aromatic ligands lacking a substituent in this position (entries 1G, H and 1J). The observed difference may be explained by the substituent in the aromatic *ortho*-position to some extent restraining the rotation of the aromatic ligand side arm in the catalytically active complex. Ligand **3k**, with the least sterically demanding *ortho*-substituent gave the best ee (98%), indicating that the observed effect is not due to a sterical effect only. The presence of a coordinating oxygen atom, as in the methoxy group of **4a**, was not required to obtain good results.

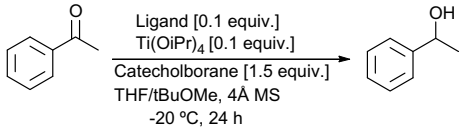
Table 4
Asymmetric reduction of acetophenone with catecholborane

Entry	Ligand	Yield[a] (%)	ee[b] (%)	Config.[c]
1A	**3a**	91	77	(*R*)
1B	**3b**	72	68	(*R*)
1C	**3c**	74	34	(*R*)
1D	**3d**	69	40	(*R*)
1E	**3e**	81	31	(*R*)
1F	**3f**	77	31	(*R*)
1G	**3g**	73	71	(*R*)
1H	**3h**	76	71	(*R*)
1I	**3i**	86	97	(*R*)
1J	**3j**	80	68	(*R*)
1K	**3k**	85	98	(*R*)
1L	**3l**	88	95	(*R*)
1M	**4a**	87	96	(*R*)
1N	**4b**	46	21	(*S*)
1O	**4c**	91	94	(*R*)
2A	**6a**[d]	43	9	(*R*)
2B	**6b**[d]	30	19	(*R*)
2C	**6c**[d]	30	16	(*S*)
3A	**7a**[d]	62	5	(*R*)
3B	**7b**[d]	57	11	(*R*)
3C	**7c**[d]	40	*rac*	—
4A	**10a**[d]	46	4	(*R*)
4B	**10b**[d]	46	20	(*R*)
4C	**10c**[d]	46	5	(*S*)

[a] Isolated yields.
[b] Determined by HPLC on Chiralcel OD-H.
[c] Determined by order of elution on Chiralcel OD-H.
[d] Reaction performed without 4 Å molecular sieves.

The introduction of a methyl group at the bridgehead position between the hydroxy groups, **4b**, resulted in a considerably lower yield and ee (entry 1N), when compared to **4a**. A reversal in enantioselectivity was observed. Obviously, the methyl group at this position disturbed the structure of the catalyst through sterical interactions, thereby forming a less selective catalyst. Previously, a similar result was obtained with the same ligand **4b** in the diethylzinc addition to benzaldehyde.[24] Investigations of 1:1 mixtures of **4b** and Ti(O*i*Pr)$_4$ with NMR spectroscopy showed that several complexes were formed, in contrast to the single complex that was formed when employing **4a** or **3g**, respectively.[23] However, the introduction of a methyl group at the 4-position (**4c**, entry 1O) gave results comparable to **4a**, implying that this may be a good attachment point for covalent anchoring of the ligands on solid support.

Poor results were obtained with the 2,5 substituted BODOL analogues (2,5-BODOLs). Amongst these, the best results, 19% and 20% ee were obtained with the naphthyl-substituted ligands **6b** and **10b**, respectively.



The use of 4 Å molecular sieves together with the 2,5-BODOLs was excluded due to the observed water elimination of the ligands. Treatment of ligands **6b** and **7b** at conditions similar to those used for the preparation of the titanium complexes (molecular sieves in toluene for 2 h at room temperature followed by heating at 45 °C for 90 min) resulted in the decomposition of the ligands. The major decomposition product of **7b**, diene **17** (Fig. 9), was isolated in 49% yield. The dehydration of the ligands is probably due to the weak acidity of the molecular sieves. Treatment of a solution of **7b** with a catalytic amount of PTS gave a similar result, as apparent by TLC

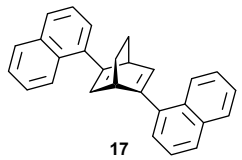
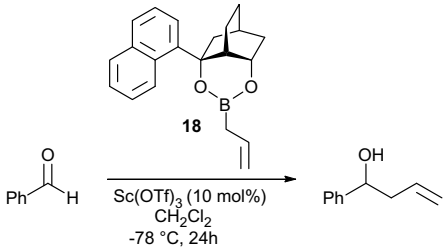


Figure 9.

analysis. It should be noted that bicyclic dienes of this type together with rhodium have been used as efficient asymmetric catalysts.[5,6,33–35] Thus, diene **17** may be valuable as a ligand itself.

During our work we learnt that the quality of the CBH/THF solutions varied considerably, resulting in drastically different yields and enantioselectivities when changing bottles. Therefore, when performing the screening of the ligands in Table 4, the same CBH solution in THF was used for all experiments. Naturally, this inconsistency in results when employing different solutions of CBH constitutes a serious weakness of the method as such. Attempts were made to increase the reproducibility of the reaction. By using solutions of CBH in toluene, it was found that the addition of DMS or *t*BuOMe to the reaction mixtures significantly improved the resulting enantioselectivities. The reduction of acetophenone, using anisyl-BODOL **4a** as ligand and a solution of CBH in toluene, resulted in 71% ee when toluene was used as the only solvent. Addition of DMS or *t*BuOMe (30% of total solvent volume) resulted in 96% and 97% ee, respectively.

Since the 2,6-BODOL ligands can easily be synthesized on a larger scale, they may also be used as reagents in stoichometric amounts. The $Sc(OTf)_3$-catalyzed allylboration of aldehydes using the Hoffman camphor-based allylboronates was reported by Hall et al. to give homoallylic alcohols of up to 98% ee.[36] Allylboronic ester **18** was synthesized and tested as allylation reagent in this reaction (Scheme 5).



Scheme 5.

The addition to benzaldehyde gave (1*S*)-1-phenyl-3-buten-1-ol of 80% ee in 59% yield. This initial result indicates that there may be a potential to obtain good results with further optimization of the reaction conditions or by using other 2,6-BODOLs than **3i** for the preparation of allylboration reagents.

3. Conclusion

In conclusion, an improved and highly selective synthesis of the BODOL ligands has been presented and several new ligands have been synthesized and tested as chiral catalysts. So far, the most successful ligands amongst these were the 2,6-BODOLs, in particular, those with an aromatic side arm with a substituent at the *ortho*-position. The application of the 2,5-BODOLs in the CBH reduction resulted in modest enantioselectivities and were considered less promising than the 2,6-BODOLs. However, for further development of the 2,5-BODOL ligand system, the hydroxyl ketones **9** and **14a** are useful intermediates for the synthesis of aminoalcohol derivatives.

The 2,6-BODOLs are easily prepared in two steps from bicyclo[2.2.2]octan-2,6-dione, for which a large scale procedure (0.5 kg scale) was recently reported.[37] Thus, the 2,6-BODOL ligands are easily accessible and have a high potential in the field of asymmetric catalysis. Further testing in various reactions will be performed in due course.

4. Experimental

4.1. General methods

Materials were obtained from commercial suppliers and used without further purification unless otherwise stated. 1 M solutions of the butyl-, isopropyl-, c-hexyl-, 1-naphthyl-, 2-methylphenyl- and 2-ethylphenyl magnesium bromides were freshly prepared from the corresponding alkyl- or aryl bromides. All solvents were dried over 4 Å for 24 h prior to use. GC analyses were performed with a Factor Four capillary column (30 m × 0.25 mm, 0.25 μm film thickness). Enantiomeric purities were analyzed by HPLC on a Chiralcel OD-H column (250 × 4.6 i.d., 5 μm) or a (*R*,*R*)-Whelk-O1 column (250 × 4.0 i.d., 5 μm). Optical rotations were measured at 22 °C and are given in 10^{-1} deg cm^2 g^{-1}. NMR spectra were recorded at 400 MHz or 300 MHz (^1H) and at 100 MHz or 75 MHz (^{13}C) using the solvents as internal references. The melting points are not corrected. Column chromatography was performed on normal phase Silica Gel 60 (25–70 μm). Thin-layer chromatography was performed on precoated TLC glass plates with Silica Gel 60_{F254}, 0.25 mm. After elution, the plates were impregnated 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) and the compounds were visualized upon heating.

4.1.1. Typical procedure A. (1*R*,2*R*,4*S*,6*S*)-2-Methyl-bicyclo-[2.2.2]octane-2,6-diol 3a

A solution of MeMgBr (1 equiv, 3.0 M in ether, 3.57 mmol) was added to a mixture of **1** (500 mg, 3.57 mmol) in ether (40 mL) at rt under an argon atmosphere. The magnesium salt precipitated and another portion of MeMgBr (1.5 equiv, 3.0 M in ether, 5.36 mmol) was added. The resulting mixture was stirred at rt for 1 h whereafter aqueous saturated NH_4Cl (50 mL) was added. Stirring at rt was continued for 10 min and the mixture was worked up as follows: the phases were separated and the water phase was extracted with EtOAc (3 × 25 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed at reduced pressure.

The residue was purified by column chromatography (SiO_2, heptane–EtOAc 33:67, TLC R_f = 0.34) to give **3a** (554 mg, 99%) as a white solid: mp 193–195 °C; $[\alpha]_D$ = +39 (*c* 0.50, *t*BuOMe); IR (KBr) 3319 $cm^{-1;}$ ^1H NMR (300 MHz, C_6D_6) δ 4.21 (d, *J* = 6.5 Hz, 1H), 4.08 (s, 1H), 3.93–3.81 (m, 1H), 1.97–1.84 (m, 1H), 1.75 (dd, *J* = 13.9, 2.7 Hz, 1H), 1.70–1.50 (m, 3H), 1.43 (dt, *J* = 13.7, 2.7 Hz, 1H), 1.40–1.26 (m, 1H), 1.16 (s, 3H), 1.10–0.94 (m, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 73.1, 71.4, 45.4, 42.1, 38.0, 30.9, 26.7, 23.4, 21.5; HRMS (FAB+, direct inlet) [M+H] calcd for $C_9H_{17}O_2$: 157.1229; found 157.1225. $C_9H_{16}O_2$ requires C, 69.19; H, 10.32. Found: C, 69.16; H, 10.38.

4.1.2. (1*R*,2*R*,4*S*,6*S*)-2-Ethyl-bicyclo[2.2.2]octane-2,6-diol 3b

The title compound was synthesized from **1** (500 mg, 3.57 mmol) and EtMgBr (2.5 equiv, 1.0 M in THF, 8.9 mmol) following procedure A. The residue was purified by column chromatography (SiO_2, heptane–EtOAc 50:50, TLC R_f = 0.34) to give **3b** (430 mg, 71%) as a white solid: mp 62–65 °C; $[\alpha]_D$ = +45.2 (*c* 1.00, *t*BuOMe); IR (KBr) 3263 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 4.09 (d, *J* = 4.5 Hz, 1H), 3.91 (br s, 1H), 3.88–3.80 (m, 1H), 2.00–1.87 (m, 1H), 1.75–1.52 (m, 4H), 1.50–1.19 (m, 4H), 1.10–0.99 (m, 3H), 0.96 (t,

J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 74.8, 71.3, 44.6, 39.3, 38.4, 35.5, 26.5, 23.6, 21.0, 7.7; HRMS (FAB+, direct inlet) [M+H] calcd for $C_{10}H_{19}O_2$: 171.1385; found 171.1382. $C_{10}H_{18}O_2$ requires C, 70.55; H, 10.66. Found: C, 70.62; H, 10.73.

4.1.3. (1*R*,2*R*,4*S*,6*S*)-2-Butyl-bicyclo[2.2.2]octane-2,6-diol 3c

The title compound was synthesized from **1** (200 mg, 1.43 mmol) and BuMgBr (2.5 equiv, 1.0 M in THF, 3.6 mmol) following procedure A. The residue was purified by column chromatography (SiO_2, heptane–EtOAc 67:33, TLC R_f = 0.30) to give **3c** (95 mg, 33%) as a transparent oil: $[\alpha]_D$ = +40 (*c* 0.60, *t*BuOMe); IR (neat) 3319 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 3.95–3.78 (m, 2H), 3.68 (br s, 1H), 2.03–1.88 (m, 1H), 1.77–1.53 (m, 4H), 1.52–1.23 (m, 8H), 1.11–0.99 (m, 3H), 0.95 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 74.8, 71.4, 45.0, 43.2, 39.8, 38.4, 26.6, 25.6, 24.1, 23.6, 21.1, 14.8; HRMS (FAB+, direct inlet) [M+H] calcd for $C_{12}H_{23}O_2$: 199.1698; found 199.1694.

4.1.4. (1*R*,2*S*,4*S*,6*S*)-2-Isopropyl-bicyclo[2.2.2]octane-2,6-diol 3d

The title compound was synthesized from **1** (500 mg, 3.57 mmol) and *i*PrMgBr (2.5 equiv, 1 M in THF, 8.9 mmol) following procedure A. The residue was purified by column chromatography (SiO_2, heptane–EtOAc 67:33, TLC R_f = 0.36) to give **3d** (83 mg, 13%) as a white solid: mp 108–115 °C; $[\alpha]_D$ = +63.7 (*c* 1.00, *t*BuOMe); IR (KBr) 3300 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 3.94–3.81 (m, 1H), 3.34 (d, J = 6.0 Hz, 1H), 3.25 (br s, 1H), 2.12–1.96 (m, 1H), 1.93–1.87 (m, 1H), 1.75–1.62 (m, 3H), 1.57–1.30 (m, 3H), 1.23–1.05 (m, 3H), 1.02 (dd, J = 6.7, 2.5 Hz, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 76.0, 71.4, 44.4, 37.9, 37.9, 36.7, 26.7, 23.7, 20.4, 17.1, 15.7; HRMS (FAB+, direct inlet) [M+H] calcd for $C_{11}H_{21}O_2$: 185.1542; found 185.1548. $C_{11}H_{20}O_2$ requires C, 71.70; H, 10.94. Found: C, 71.79; H, 10.88.

4.1.5. (1*R*,2*S*,4*S*,6*S*)-2-Cyclohexyl-bicyclo[2.2.2]octane-2,6-diol 3e

The title compound was synthesized from **1** (1.00 g, 7.14 mmol) and *c*-HexMgBr (2.5 equiv, 1 M in THF, 17.8 mmol) following procedure A. The residue was purified by column chromatography (SiO_2, heptane–EtOAc 67:33, TLC R_f = 0.39) to give **3e** (327 mg, 20%) as a white solid: mp 106–112 °C; $[\alpha]_D$ = +64 (*c* 0.70, *t*BuOMe); IR (KBr) 3265 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 3.78 (br s, 1H), 3.29 (br s, 1H), 3.13 (br s, 1H), 2.03–1.89 (m, 1H), 1.90–1.39 (m, 10H), 1.38–0.95 (m, 10H); ^{13}C NMR (75 MHz, C_6D_6) δ 76.1, 71.4, 47.3, 44.1, 38.1, 37.2, 27.6, 27.5, 27.3, 27.1, 26.6, 25.3, 23.8, 20.4; HRMS (FAB+, direct inlet) [M+H] calcd for $C_{14}H_{25}O_2$: 225.1855; found 225.1845. $C_{14}H_{24}O_2$ requires C, 74.95; H, 10.78. Found: C, 74.87; H, 10.85.

4.1.6. (1*R*,2*R*,4*S*,6*S*)-2-Vinylbicyclo[2.2.2]octane-2,6-diol 3f

The title compound was synthesized from **1** (500 mg, 3.57 mmol) and vinylMgBr (2.5 equiv, 1.0 M in THF, 8.9 mmol) following procedure A. The residue was purified by column chromatography (SiO_2, heptane–EtOAc 67:33, TLC R_f = 0.26) to give **3f** (529 mg, 88%) as a white solid: mp 68–70 °C; $[\alpha]_D$ = +76 (*c* 0.56, *t*BuOMe); IR (KBr) 3300 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 5.87 (dd, J = 17.2, 10.7 Hz, 1H), 5.32 (dd, J = 17.2, 1.5 Hz, 1H), 5.00 (dd, J = 10.7, 1.5 Hz, 1H), 4.08 (d, J = 6.6 Hz, 1H), 4.00 (s, 1H), 3.92–3.77 (m, 1H), 2.02–1.88 (m, 1H), 1.80–1.52 (m, 5H), 1.47–1.28 (m, 1H), 1.15–0.95 (m, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 145.6, 112.4, 75.2, 71.0, 42.6, 41.6, 38.2, 26.2, 23.5, 20.9; HRMS (FAB+, direct inlet) [M+H] calcd for $C_{10}H_{17}O_2$: 169.1229; found 169.1245. $C_{10}H_{16}O_2$ requires C, 71.39; H, 9.59. Found: C, 71.25; H, 9.60.

4.1.7. (1*R*,2*R*,4*S*,6*S*)-2-Phenyl-bicyclo[2.2.2]octane-2,6-diol 3g

The title compound was synthesized from **1** (200 mg, 1.43 mmol) and PhMgBr (2.5 equiv, 1.0 M in THF, 3.6 mmol) following procedure A. The residue was purified by column chromatography (SiO_2, heptane–EtOAc 67:33, TLC R_f = 0.28) to give **3g** (294 mg, 94%) as a transparent oil which crystallized on standing: mp 82–86 °C (lit.[21] mp 84–87 °C); $[\alpha]_D$ = +69.9 (*c* 1.36, $CHCl_3$) (lit.[21] $[\alpha]_D$ = +71 (*c* 2.2, $CHCl_3$)). ^{1}H NMR and ^{13}C NMR data were identical to those reported.[22]

4.1.8. (1*R*,2*R*,4*S*,6*S*)-2-(4-Biphenyl)-bicyclo[2.2.2]octane-2,6-diol 3h

The title compound was synthesized from **1** (500 mg, 3.57 mmol) and 4-biphenylMgBr (2.5 equiv, 0.5 M in THF, 8.9 mmol) following procedure A. The residue was purified by column chromatography (SiO_2, heptane–EtOAc 67:33, TLC R_f = 0.28) to give **3h** (927 mg, 88%) as a white solid: mp 123–130 °C; $[\alpha]_D$ = +42 (*c* 0.70, *t*BuOMe); IR (KBr) 3254 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 7.70–7.47 (m, 6H), 7.33–7.12 (m, 3H), 3.92 (s, 1H), 3.85 (br s, 2H), 2.24 (dt, J = 14.4, 2.4 Hz, 1H), 2.12–1.97 (m, 1H), 1.95 (s, 1H), 1.81 (d, J = 14.7 Hz, 1H), 1.76–1.64 (m, 2H), 1.30–0.93 (m, 4H); ^{13}C NMR (75 MHz, C_6D_6) δ 146.7, 141.0, 139.8, 128.8, 127.2, 127.1, 126.8, 126.7, 76.3, 70.6, 42.3, 42.1, 37.8, 25.9, 22.8, 20.3; HRMS (FAB+, direct inlet) [M] calcd for $C_{20}H_{22}O_2$: 294.1620; found 294.1611. $C_{20}H_{22}O_2$ requires C, 81.60; H, 7.53. Found: C, 81.56; H, 7.43.

4.1.9. (1*R*,2*R*,4*S*,6*S*)-2-(Naphthalen-1-yl)-bicyclo[2.2.2]octane-2,6-diol 3i

The title compound was synthesized from **1** (500 mg, 3.57 mmol) and 1-naphthylMgBr (2.5 equiv, 1 M in THF, 8.9 mmol) following procedure A. The residue was purified by column chromatography (SiO_2, heptane–EtOAc 67:33, TLC R_f = 0.32) to give **3i** (806 mg, 84%) as a white solid: mp 117–120 °C; $[\alpha]_D$ = +25.6 (*c* 2.30, *t*BuOMe); IR (KBr) 3263 cm^{-1}; ^{1}H NMR (400 MHz, toluene-d_8) δ 8.90 (d, J = 8.7 Hz, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.55 (dd, J = 7.3, 1.4 Hz, 1H), 7.37 (ddd, J = 8.4, 1.5 Hz, 1H), 7.29–7.23 (m, 1H), 7.22–7.13 (m, 2H), 3.80–3.71 (m, 1H), 3.70 (d, J = 9.1 Hz, 1H), 3.10 (s, 1H), 2.45 (br s, 1H), 2.16 (d, J = 12.8 Hz, 1H), 2.07–1.96 (m, 2H), 1.69 (dd, J = 12.7, 5.9 Hz, 1H), 1.64–1.56 (m, 1H), 1.34–1.21 (m, 1H), 1.12–1.02 (m, 1H), 1.01–0.92 (m, 2H); ^{13}C NMR (75 MHz, C_6D_6) δ 142.4, 136.3, 132.6, 129.7, 129.3, 129.0, 125.9, 125.8, 124.8, 123.9, 79.1, 71.3, 44.8, 40.7, 38.4, 26.8, 23.6, 21.9; HRMS (FAB+, direct inlet) [M] calcd for $C_{18}H_{20}O_2$: 268.1463; found 268.1464. $C_{18}H_{20}O_2$ requires C, 80.56; H, 7.51. Found: C, 80.69; H, 7.48.

4.1.10. (1*R*,2*R*,4*S*,6*S*)-2-(Naphthalen-2-yl)-bicyclo[2.2.2]octane-2,6-diol 3j

The title compound was synthesized from **1** (500 mg, 3.57 mmol) and 2-naphthylMgBr (2.5 equiv, 0.5 M in THF, 8.9 mmol) following procedure A. The residue was purified by column chromatography (SiO_2, heptane–EtOAc 67:33, TLC R_f = 0.23) to give **3j** (806 mg, 84%) as a white solid: mp 100–104 °C; $[\alpha]_D$ = +50 (*c* 0.50, *t*BuOMe); IR (KBr) 3248 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 7.86 (s, 1H), 7.78–7.61 (m, 4H), 7.40–7.23 (m, 2H), 4.00 (d, J = 7.3 Hz, 1H), 3.99 (s, 1H), 3.90–3.77 (m, 1H), 2.32 (dt, J = 14.4, 2.4 Hz, 1H), 2.10–1.95 (m, 2H), 1.83 (doublet of multiplets, J = 14.6 Hz, 1H), 1.77–1.65 (m, 2H), 1.18–1.16 (m, 2H), 1.06–0.85 (m, 2H); ^{13}C NMR (75 MHz, C_6D_6) δ 145.4, 133.8, 133.4, 129.1, 128.6, 128.2, 126,5, 126.5, 126.1, 125.1, 77.2, 71.2, 42.7, 42.5, 38.5, 26.6, 23.5, 20.9; HRMS (FAB+, direct inlet) [M] calcd for $C_{18}H_{20}O_2$: 268.1463; found 268.1461. $C_{18}H_{20}O_2$ requires C, 80.56; H, 7.51. Found: C, 80.59; H, 7.57.

4.1.11. (1*R*,2*R*,4*S*,6*S*)-2-*o*-Tolylbicyclo[2.2.2]octane-2,6-diol 3k

The title compound was synthesized from **1** (400 mg, 2.86 mmol) and 2-methylphenylMgBr (2.5 equiv, 1 M in THF, 7.15 mmol) following procedure A. The residue was purified by

column chromatography (SiO_2, heptane–EtOAc 75:25) to give **3k** (641 mg, 97%) as a transparent oil which crystallized on standing: TLC R_f = 0.47 (SiO_2, heptane–EtOAc 50:50); mp 109–114 °C; $[\alpha]_D$ = +41.0 (2.30, *t*BuOMe); IR (KBr) 3260 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.12–7.08 (m, 1H), 7.06–6.95 (m, 3H), 3.75 (vbr s, 2H), 3.22 (vbr s, 1H), 2.52 (s, 3H), 2.24 (br s, 1H), 2.04–1.94 (m, 2H), 1.91–1.84 (m, 1H), 1.66–1.53 (m, 2H), 1.36–1.27 (m, 1H), 1.15–1.05 (m, 1H), 0.97–0.91 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 144.9, 138.7, 133.9, 127.7, 126.3, 125.5, 78.4, 71.2, 44.1, 40.2, 38.2, 26.6, 23.6, 23.0, 21.8. $C_{15}H_{20}O_2$ requires C, 77.55, H; 8.68. Found: C, 77.52; H, 8.92.

4.1.12. (1*R*,2*R*,4*S*,6*S*)-2-(2-Ethylphenyl)bicyclo[2.2.2]octane-2,6-diol 3l

The title compound was synthesized from **1** (400 mg, 2.86 mmol) and 2-ethylphenylMgBr (2.5 equiv, 1 M in THF, 7.15 mmol) following procedure A. The residue was purified by column chromatography (SiO_2, heptane–EtOAc 75:25) to give **3l** (628 mg, 89%) as a transparent oil: TLC R_f = 0.56 (SiO_2, heptane–EtOAc 50:50); $[\alpha]_D$ = +34.1 (*c* 2.60, *t*BuOMe); IR (NaCl) 3287 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.20 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.15–7.09 (m, 2H), 7.01 (td, *J* = 7.6, 1.5 Hz, 1H), 3.86–3.76 (m, 1H), 3.41 (d, *J* = 8.4 Hz, 1H), 3.13 (dt_{AB}, *J* = 21.5, 7.4 Hz, 1H), 2.95 (d, *J* = 1.7 Hz, 1H), 2.93 (dt_{AB}, *J* = 21.5, 7.4 Hz, 1H), 2.32–2.26 (m, 1H), 2.07–1.97 (m, 3H), 1.70–1.58 (m, 2H), 1.39–1.28 (m, 1H), 1.25 (t, *J* = 7.5, 3H), 1.19–1.08 (m, 1H), 1.03–0.94 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 145.1, 144.5, 132.1, 127.6, 126.1, 125.0, 78.4, 71.1, 44.3, 40.7, 38.1, 27.4, 26.5, 23.4, 21.7, 17.0. $C_{16}H_{22}O_2$ requires C, 78.01; H, 9.00. Found: C, 78.11; H, 8.94.

4.1.13. Typical procedure B. (1*R*,2*R*,4*S*,6*S*)-2-(2-Methoxyphenyl)-bicyclo[2.2.2]octane-2,6-diol 4a

o-Anisyllithium [prepared by the addition of *n*BuLi (2.5 M in hexane, 10.7 mmol) to anisole (13.4 mmol, 1.43 mL) in THF (20 mL)] was added to a mixture of **1** (500 mg, 3.57 mmol) in ether (40 mL) at rt under an argon atmosphere. The resulting mixture was stirred at rt for 1 h whereafter aqueous saturated NH_4Cl (50 mL) was added. Stirring at rt was continued for 10 min and the mixture was worked up as follows: the phases were separated and the water phase was extracted with EtOAc (3 × 25 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed at reduced pressure. The residue was purified by column chromatography (SiO_2, heptane–EtOAc 50:50, TLC R_f = 0.26) to give **4a** (576 mg, 65%) as a white solid: mp 82–84 °C (lit.[22] mp 82–83 °C; lit.[21] 74–78 °C); $[\alpha]_D$ = +50.0 (*c* 0.70, $CHCl_3$) {lit.[21] $[\alpha]_D$ = +46 (*c* 0.68, $CHCl_3$)}. ^1H NMR data were consistent with those reported.[22]

4.1.14. (1*R*,2*R*,4*S*,6*S*)-2-(2-Methoxyphenyl)-1-methylbicyclo-[2.2.2]octane-2,6-diol 4b

The title compound was synthesized from (1*R*,4*S*,6*S*)-6-hydroxy-1-methylbicyclo[2.2.2]octan-2-one (0.10 g, 0.65 mmol) and *o*-anisyllitium (3 equiv, 1.95 mmol) following procedure B. The residue was purified by column chromatography (SiO_2, heptane–EtOAc 75:25) to give **4b** (140 mg, 82%) as a white solid. R_f = 0.43 (SiO_2, heptane–EtOAc 50:50): mp 161–166 °C (lit.[24] mp 169 °C); $[\alpha]_D$ = +62.3 (*c* 0.69, MeOH) (lit.[24] $[\alpha]_D$ = +61.9 (*c* 0.512, MeOH)). ^1H NMR data were consistent with those reported.[24]

4.1.15. (1*R*,2*R*,4*S*,6*S*)-2-(2-Methoxyphenyl)-4-methylbicyclo[2.2.2]octane-2,6-diol 4c

The title compound was synthesized from (1*R*,4*S*,6*S*)-6-Hydroxy-4-methylbicyclo[2.2.2]octan-2-one (0.10 g, 0.65 mmol) and *o*-Anisyllitium (3 equiv, 1.95 mmol) following procedure B. The residue was purified by column chromatography (SiO_2, pentane:acetone 90:10) to give **4b** (128 mg, 75%) as a white solid: R_f = 0.26 (SiO_2, heptane–EtOAc 50:50); mp 82–85 °C (lit.[24] 85–87 °C); $[\alpha]_D$ = +45.2 (*c* 0.51, MeOH) (lit.[24] $[\alpha]_D$ = +46.7 (*c* 0.6, MeOH). ^1H NMR data were consistent with those reported.[24]

4.1.16. Typical procedure C. (1*S*,2*S*,4*S*,5*S*)-2-Phenylbicyclo-[2.2.2]octane-2,5-diol 6a

A solution of PhMgBr (2.5 equiv, 1.0 M in THF, 4.90 mmol) was added to a mixture of **8** (275 mg, 1.96 mmol) in ether (15 mL) at rt under an argon atmosphere. Water (2.5 equiv, 88 μL, 4.90 mmol) was added and the mixture was stirred for 15 min before another portion of PhMgBr (2.5 equiv, 1.0 M in THF, 4.90 mmol) was added. Water (2.5 equiv, 88 μL, 4.90 mmol) was again added and the mixture was stirred for another 15 min before the last portion of PhMgBr (2.5 equiv, 1.0 M in THF, 4.90 mmol) was added. The resulting slurry was stirred at rt for 30 min and then aqueous saturated NH_4Cl (20 mL) was added. Stirring was continued for 10 min and the mixture was worked up as follows: the phases were separated and the water phase was extracted with EtOAc (3x30 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed at reduced pressure. The residue was purified by column chromatography (SiO_2, heptane–EtOAc 67:33) to give **6a** (231 mg, 54%) as a transparent oil which crystallized on standing: TLC R_f = 0.31 (SiO_2, heptane–EtOAc 50:50); mp 80–86 °C; $[\alpha]_D$ = −111 (*c* 0.55, *t*BuOMe); IR (KBr) 3432, 3348 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.48 (d, *J* = 8.0 Hz, 2H), 7.21 (t, *J* = 7.9 Hz, 2H), 7.11 (t, *J* = 7.1 Hz, 1H), 3.76–3.65 (m, 1H), 3.27 (s, 1H), 3.19 (d, *J* = 5.8 Hz, 1H), 2.18 (dd, *J* = 14.7, 4.0 Hz, 1H), 2.10 (d, *J* = 14.5 Hz, 1H), 1.94 (s, 1H), 1.92 (d, *J* = 15.0 Hz, 1H), 1.83 (br s, 1H), 1.56 (ddd, *J* = 14.4, 8.9, 1.3 Hz, 1H), 1.27–1.16 (m, 2H), 1.09–0.94 (m, 2H); ^{13}C NMR (75 MHz, C_6D_6) δ 147.7, 128.6, 127.4, 126.8, 74.6, 68.3, 37.0, 36.0, 33.5, 33.0, 22.5, 21.6; HRMS (FAB+, direct inlet) [M] calcd for $C_{14}H_{18}O_2$: 218.1307; found 218.1302. $C_{14}H_{18}O_2$ requires C, 77.03; H, 8.31. Found: C, 76.87; H, 8.24.

4.1.17. (1*S*,2*S*,4*S*,5*S*)-2-(Naphthalen-1-yl)bicyclo[2.2.2]octane-2,5-diol 6b

The title compound was synthesized from **8** (590 mg, 4.21 mmol), 1-naphthylMgBr (3 × 2.5 equiv, 1 M in THF, 31.6 mmol) and water (3 × 2.5 equiv, 31.6 mmol) following procedure C. The residue was purified by column chromatography (SiO_2, heptane–EtOAc 80:20) to give **6b** (449 mg, 40%) as a white solid: TLC R_f = 0.41 (SiO_2, heptane–EtOAc 50:50); mp 72–78 °C; $[\alpha]_D$ = −74 (*c* 0.50, *t*BuOMe); IR (KBr) 3362 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 9.01 (d, *J* = 8.7 Hz, 1H), 7.69 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.40–7.33 (m, 1H), 7.32–7.23 (m, 2H), 7.20 (d, *J* = 7.8 Hz, 1H), 3.74–3.65 (m, 1H), 3.20 (d, *J* = 7.6 Hz, 1H), 3.05 (s, 1H), 2.57 (d, *J* = 14.3 Hz, 1H), 2.40 (br s, 1H), 2.12 (dt, *J* = 14.6, 3.2 Hz, 1H), 1.86 (d, *J* = 14.8 Hz, 1H), 1.80–1.73 (m, 1H), 1.59 (ddd, *J* = 14.6, 8.8, 1.7 Hz, 1H), 1.38–1.25 (m, 1H), 1.20–1.03 (m, 2H), 1.01–0.90 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 141.9, 136.3, 133.0, 129.6, 129.3, 129.2, 125.9, 125.7, 124.7, 124.1, 76.6, 68.4, 37.6, 35.8, 33.4, 33.1, 22.7, 22.5; HRMS (ES+) [M] calcd for $C_{18}H_{20}O_2Na$: 291.1361; found 291.1321. $C_{18}H_{20}O_2$ requires C, 80.56; H, 7.51. Found: C, 80.43; H, 7.46.

4.1.18. (1*S*,2*S*,4*S*,5*S*)-2-(2-Methoxyphenyl)bicyclo[2.2.2]octane-2,5-diol 6c

The title compound was synthesized from **8** (970 mg, 6.92 mmol) and *o*-anisyllitium (4 equiv, 27.7 mmol) following procedure B. The residue was purified by column chromatography (SiO_2, heptane–EtOAc 60:40) to give **6c** (1.32 g, 77%) as a white solid: TLC R_f = 0.26 (SiO_2, heptane–EtOAc 50:50); mp 128–129 °C; $[\alpha]_D$ = −59 (*c* 0.52, *t*BuOMe); IR (KBr) 3501, 3457 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.17 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.02 (td, *J* = 8.2, 1.6 Hz, 1H), 6.81 (td, *J* = 7.6, 1.1 Hz, 1H), 6.44 (dd, *J* = 8.2, 0.9 Hz, 1H), 4.53 (s, 1H), 4.00–3.91 (m, 1H), 3.87 (d, *J* = 10.6 Hz, 1H), 3.02

(s, 3H), 2.50 (dd, J = 14.8, 2.6 Hz, 1H), 2.37 (doublet of multiplets, J = 14.7 Hz, 1H), 2.27 (s, 1H), 2.09–2.03 (m, 1H), 1.98 (d, J = 15.0, 1H), 1.77 (ddd, J = 14.3, 8.8, 1.8 Hz, 1H), 1.35–1.26 (m, 1H), 1.26–1.17 (m, 1H), 1.16–1.05 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 158.3, 134.3, 128.6, 127.4, 121.2, 112.2, 76.3, 68.5, 55.0, 35.6, 34.3, 34.1, 33.4, 22.9, 22.1; HRMS (FAB+, direct inlet) [M] calcd for $C_{15}H_{20}O_3$: 248.1412; found 248.1411. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.12. Found: C, 72.47; H, 8.06.

4.1.19. (1*S*,2*S*,4*S*,5*S*)-2,5-Diphenylbicyclo[2.2.2]octane-2,5-diol 7a

The title compound was synthesized from **9a** (175 mg, 0.81 mmol), PhMgBr (3 × 2.5 equiv, 1.0 M in THF, 6.08 mmol) and water (3 × 2.5 equiv, 6.08 mmol) following procedure C. The residue was purified by column chromatography (SiO_2, heptane–EtOAc 90:10, then 50:50 when **7a** started to elute) to give **7a** (170 mg, 71%) as a white solid: TLC R_f = 0.63 (SiO_2, heptane–EtOAc 50:50); mp 147–149 °C; $[\alpha]_D$ = −87 (c 0.40, tBuOMe); IR (KBr) 3387, 3277 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 7.4 Hz, 4H), 7.41 (t, J = 7.2 Hz, 4H), 7.31 (t, J = 7.3 Hz), 2H), 3.53 (s, 2H), 2.58 (dd, J = 14.8, 4.1 Hz), 2H), 2.41 (br s, 2H), 2.32 (dd, J = 14.7, 1.6 Hz, 2H), 1.44 (br s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3, 128.5, 127.4, 126.2, 74.5, 37.8, 37.4, 21.5; HRMS (FAB+, direct inlet) [M] calcd for $C_{20}H_{22}O_2$: 294.1620; found 294.1619. $C_{20}H_{22}O_2$ requires C, 81.60; H, 7.53. Found: C, 81.48; H, 7.49.

4.1.20. (1*S*,2*S*,4*S*,5*S*)-2,5-Di(naphthalen-1-yl)bicyclo[2.2.2]-octane-2,5-diol 7b

The title compound was synthesized from **9b** (350 mg, 1.31 mmol), 1-naphthylMgBr (3 × 2.5 equiv, 1 M in THF, 9.83 mmol) and water (3 × 2.5 equiv, 9.83 mmol) following procedure C. The residue was purified by column chromatography (SiO_2, heptane–EtOAc 85:15) to give **7b** (487 mg, 94%) as a white solid: TLC R_f = 0.66 (SiO_2, heptane–EtOAc 50:50); mp 147–151 °C; $[\alpha]_D$ = −110 (c 0.45, tBuOMe); IR (KBr) 3254 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 9.07 (d, J = 8.7 Hz, 2H), 7.73 (d, J = 8.1 Hz, 2H), 7.64 (d, J = 7.8 Hz, 2H), 7.51–7.44 (m, 2H), 7.39–7.32 (m, 2H), 7.26 (d, J = 6.2 Hz, 2H), 7.22 (t, J = 7.5 Hz, 2H), 3.86 (br s, 2H), 2.81 (d, J = 13.7 Hz, 2H), 2.41 (br s, 2H), 1.95 (d, J = 14.8 Hz, 2H), 1.43–1.30 (m, 2H), 1.16–1.01 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 141.70, 136.4, 133.2, 129.6, 129.4, 129.2, 125.9, 125.8, 124.7, 124.2, 76.32, 39.6, 37.1, 22.8; HRMS (ES+) [M] calcd for $C_{28}H_{26}O_2Na$: 417.1831; found 417.1844. $C_{28}H_{26}O_2$ requires C, 85.25; H, 6.64. Found: C, 85.15; H, 6.61.

4.1.21. (1*S*,2*S*,4*S*,5*S*)-2,5-Bis(2-methoxyphenyl)bicyclo-[2.2.2]octane-2,5-diol 7c

The title compound was synthesized from **9c** (970 mg, 3.94 mmol) and *o*-anisyllithium (4 equiv, 15.8 mmol) following procedure B. The residue was purified by column chromatography (SiO_2, heptane–EtOAc 67:33, TLC R_f = 0.37) to give **7c** (873 mg, 63%) as a white solid: mp 162–167 °C; $[\alpha]_D$ = −24 (c 0.32, CH_2Cl_2); IR (KBr) 3549 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 7.40 (d, J = 7.7 Hz, 2H), 7.10 (t, J = 8.1 Hz, 2H), 6.88 (t, J = 7.5 Hz, 2H), 6.57 (d, J = 8.2 Hz, 2H), 4.86 (s, 2H), 3.21 (s, 6H), 3.23–3.17 (m, 2H), 2.62 (br s, 2H), 2.34 (dd, J = 15.0, 2.3 Hz, 2H), 1.39–1.24 (m, 4H); ^{13}C NMR (75 MHz, C_6D_6) δ 159.1, 135.2, 128.6, 127.6, 120.9, 112.7, 75.5, 55.3, 37.3, 36.9, 22.2; HRMS (FAB+, direct inlet) [M] calcd for $C_{22}H_{26}O_4$: 354.1831; found 354.1836. $C_{22}H_{26}O_4$ requires C, 74.55; H, 7.39. Found: C, 74.63; H, 7.43.

4.1.22. (1*R*,2*S*,4*R*,5*S*)-2,5-Diphenylbicyclo[2.2.2]oct-7-ene-2,5-diol 10a

The title compound was synthesized from (+)-**13** (1.00 g, 7.35 mmol) of >98% ee (HPLC, Chiralcel OD-H), PhMgBr (3 × 2.5 equiv, 1.0 M in THF, 55.1 mmol) and water (3 × 2.5 equiv, 55.1 mmol) following procedure C. The residue was purified by column chromatography (SiO_2, heptane–EtOAc 90:10) to give **10a** (492 mg, 23%) as a white solid: TLC R_f = 0.69 (SiO_2, heptane–EtOAc 50:50); mp 187–189 °C (from toluene); $[\alpha]_D$ = +74 (c 0.50, $CHCl_3$). ^{1}H NMR data were consistent with those reported for (±)-**10a** (see below).

4.1.23. (1*S*,2*R*,4*S*,5*R*)-2,5-Di(naphthalen-1-yl)bicyclo[2.2.2]oct-7-ene-2,5-diol 10b

The title compound was synthesized from (−)-**13** (900 mg, 6.61 mmol) of >98% ee, 1-naphthylMgBr (3 × 2.5 equiv, 1 M in THF, 49.6 mmol) and water (3 × 2.5 equiv, 49.6 mmol) following procedure C. The residue was purified by column chromatography (SiO_2, heptane–EtOAc 90:10) to give **10b** (318 mg, 12%) as a white solid: TLC R_f = 0.82 (SiO_2, pentane:ether 40:60); mp 148–151 °C (melt and decomposition); $[\alpha]_D$ = +13.7 (c 1.53, $CHCl_3$); IR (KBr) 3227 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (d, J = 8.7 Hz, 2H), 7.88 (dd, J = 8.0, 1.4 Hz, 2H), 7.78 (d, J = 8.1 Hz, 2H), 7.60–7.54 (m, 2H), 7.54–7.46 (m, 4H), 7.38 (t, J = 8.0 Hz, 2H), 6.40 (dd, J = 4.4, 3.2 Hz, 2H), 3.44–3.38 (m, 2H), 3.34 (dd, J = 14.1, 3.1 Hz, 2H), 3.04 (s, 2H), 2.01 (dd, J = 14.0, 2.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 135.6, 132.7, 131.7, 129.4, 129.1, 127.9, 125.9, 125.9, 124.9, 123.2, 78.3, 43.7, 40.7; HRMS (FAB+, direct inlet) [M] calcd for $C_{28}H_{24}O_2Na$: 415.1674; found 415.1668. $C_{20}H_{24}O_4$ requires C, 85.68; H, 6.16. Found: C, 85.40; H, 6.08.

4.1.24. (1*S*,2*R*,4*S*,5*R*)-2,5-Bis(2-methoxyphenyl)bicyclo-[2.2.2]oct-7-ene-2,5-diol 10c

The title compound was synthesized from (−)-**13** (400 mg, 2.94 mmol) of >98% ee (HPLC, Chiralcel OD-H) and *o*-Anisyllithium (4 equiv, 11.8 mmol) following procedure B. The residue was purified by column chromatography (SiO_2, heptane–EtOAc 85:15 to 33:67) to give **10c** (128 mg, 12%) as a white solid: TLC R_f = 0.38 (SiO_2, heptane–EtOAc 50:50); mp 89–93 °C (melt and decomp.); $[\alpha]_D$ = −147 (c 0.23, CH_2Cl_2); IR (KBr) 3380 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.17 (m, 4H), 6.95–6.87 (m, 4H), 6.17 (dd, J = 4.5, 3.1 Hz, 2H), 4.20 (s, 2H), 3.93 (s, 6H), 3.22–3.15 (m, 2H), 2.92 (dd, J = 14.2, 2.6 Hz, 2H), 1.97 (dd, J = 14.2, 3.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 136.7, 133.0, 128, 1, 126.9, 120.5, 111.5, 76.7, 55.8, 41.5, 38.3; HRMS (FAB+, direct inlet) [M] calcd for $C_{20}H_{24}O_4$: 352.1675; found 352.1671. $C_{20}H_{24}O_4$ requires C, 74.98; H, 6.86. Found: C, 74.84; H, 6.73.

4.1.25. (1*R*,2*S*,4*R*,5*S*)-2-(Naphthalen-1-yl)bicyclo[2.2.2]oct-7-ene-2,5-diol 12

The title compound was synthesized from **11** (200 mg, 1.45 mmol) of >99% ee, 1-naphthylMgBr (3 × 2.5 equiv, 1 M in THF, 10.9 mmol) and water (3 × 2.5 equiv, 10.9 mmol) following procedure C. The residue was purified by column chromatography (SiO_2, heptane–EtOAc 75:25) to give **12** (54 mg, 14%) as a white solid: TLC R_f = 0.32 (SiO_2, heptane–EtOAc 50:50); mp 75–78 °C; $[\alpha]_D$ = −44 (c 0.45, tBuOMe); IR (KBr) 3381 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 8.84 (d, J = 8.8 Hz, 1H), 7.68 (doublet of multiplets, J = 8.1 Hz, 1H), 7.57 (dd, J = 6.3, 2.9 Hz, 1H), 7.41–7.34 (m, 1H), 7.33–7.28 (m, 1H), 7.20–7.16 (m, 2H), 6.20–6.14 (m, 1H), 5.81–5.75 (m, 1H), 3.79 (d, J = 9.7 Hz, 1H), 2.92 (dd, J = 13.9, 2.7 Hz, 1H), 2.81–2.76 (m, 1H), 2.45–2.39 (m, 1H), 2.06 (dt, J = 13.7, 2.4 Hz, 1H), 1.86–1.58 (m, 4H); ^{13}C NMR (100 MHz, C_6D_6) δ 145.0, 136.0, 135.3, 132.4, 131.8, 129.5, 128.9, 128.4, 125.94, 125.9, 124.9, 123.4, 78.5, 68.2, 42.7, 39.7, 38.0, 32.8; HRMS (FAB+, direct inlet) [M] calcd for $C_{18}H_{18}O_2Na$: 289.1204; found 289.1220.

4.1.26. Typical procedure D. (1*S*,4*S*,5*S*)-5-Hydroxy-5-phenylbicyclo[2.2.2]octan-2-one 9a

N-Methylmorpholine N-oxide (281 mg, 2.40 mmol), 3 Å crushed molecular sieves (827 mg) and tetrapropylammoniumper-

ruthenate (21 mg, 5 mol %) were added to a solution of diol **6a** (261 mg, 1.20 mmol) in CH_2Cl_2 (24 mL) at rt under an argon atmosphere. The resulting mixture was stirred at rt for 1 h and then filtered through a pad of silica (bottom layer) and Celite (top layer), rinsed with EtOAc whereafter the solvent was removed at reduced pressure.

The residue was purified by column chromatography (SiO_2, heptane–EtOAc 80:20) to give **9a** (243 mg, 94%) as a transparent oil: TLC R_f = 0.43 (SiO_2, heptane–EtOAc 50:50); $[\alpha]_D = -20$ (*c* 0.30, *t*BuOMe); IR (NaCl) 3418, 1715 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.34–7.29 (m, 2H), 7.19–7.13 (m, 2H), 7.12–7.06 (m, 1H), 3.02 (dt, *J* = 18.5, 3.0 Hz, 1H), 2.28 (p, *J* = 3.0 Hz, 1H), 2.18 (dd, *J* = 14.7, 2.7 Hz, 1H), 2.03 (s, 1H), 2.03–1.99 (m, 1H), 1.83 (dd, *J* = 18.7, 2.6 Hz, 1H), 1.79 (dt, *J* = 14.8, 3.0 Hz, 1H), 1.37–1.27 (m, 1H), 1.26–1.10 (m, 2H), 1.04–0.94 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 215.1, 147.3, 128.7, 127.7, 126.6, 74.1, 44.1, 41.0, 40.9, 40.3, 21.9, 20.9; HRMS (FAB+, direct inlet) [M] calcd for $C_{14}H_{16}O_2$: 216.1150; found 216.1162. $C_{14}H_{16}O_2$ requires C, 77.75; H, 7.46. Found: C, 77.68; H, 7.37. Racemic **9a** has been isolated previously although the configuration of the phenyl group was not determined.[38]

4.1.27. (1*S*,4*S*,5*S*)-5-Hydroxy-5-(naphthalen-1-yl)bicyclo-[2.2.2]octan-2-one 9b

The title compound was synthesized from **6b** (448 mg, 1.67 mmol) following procedure D. The residue was purified by column chromatography (SiO_2, heptane–EtOAc 67:33) to give **9b** (409 mg, 92%) as a white solid: TLC R_f = 0.47 (SiO_2, heptane–EtOAc 50:50); mp 163–166 °C; $[\alpha]_D = -22$ (*c* 0.51, *t*BuOMe); IR (KBr) 3356, 1709 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 8.79 (d, *J* = 8.6 Hz, 1H), 7.68 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.36–7.26 (m, 2H), 7.15–7.10 (m, 2H), 3.04 (dt, *J* = 18.3, 3.0 Hz, 1H), 2.57–2.51 (m, 1H), 2.24 (p, *J* = 2.9 Hz, 1H), 2.18–2.13 (m, 2H), 1.87 (dd, *J* = 18.4, 2.6 Hz, 1H), 1.49 (s, 1H), 1.37–1.22 (m, 2H), 1.18–1.02 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 214.2, 141.4, 136.2, 132.7, 129.7, 129.6, 128.8, 126.1, 126.0, 124.5, 123.9, 75.8, 44.1, 42.8, 39.9, 39.1, 21.9, 21.8; HRMS (ES+) [M+H] calcd for $C_{18}H_{19}O_2$: 267.1385; found 267.1374. $C_{18}H_{18}O_2$ requires C, 81.17; H, 6.81. Found: C, 81.08; H, 6.74.

4.1.28. (1*S*,4*S*,5*S*)-5-Hydroxy-5-(2-methoxyphenyl)bicyclo-[2.2.2]octan-2-one 9c

The title compound was synthesized from **6c** (219 mg, 0.88 mmol) following procedure D. The residue was purified by column chromatography (SiO_2, heptane–EtOAc 67:33, TLC R_f = 0.57) to give **9c** (210 mg, 97%) as a white solid: mp 76–79 °C; $[\alpha]_D = -4.9$ (*c* 0.50, *t*BuOMe); IR (KBr) 3425, 1730 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.08 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.03 (td, *J* = 7.6, 1.6 Hz, 1H), 6.80 (td, *J* = 7.6, 1.1 Hz, 1H), 6.43 (dd, *J* = 8.2, 0.9 Hz, 1H), 4.19 (s, 1H), 3.25 (dt, *J* = 18.3, 2.7 Hz, 1H), 2.98 (s, 3H), 2.50 (p, *J* = 2.9 Hz, 1H), 2.38 (p, *J* = 3.0 Hz, 1H), 2.28–2.23 (m, 2H), 1.98 (dd, *J* = 18.3, 2.7 Hz, 1H), 1.50–1.05 (m, 4H); ^{13}C NMR (75 MHz, C_6D_6) δ 214.1, 158.2, 134.0, 128.8, 127.1, 121.1, 112.2, 75.2, 54.9, 44.1, 40.0, 39.8, 38.8, 22.0, 21.7; HRMS (FAB+, direct inlet) [M] calcd for $C_{15}H_{18}O_3$: 246.1256; found 246.1251. $C_{15}H_{18}O_3$ requires C, 73.15; H, 7.37. Found: C, 73.08; H, 7.28.

4.2. Addition of PhMgCl to (±)-13, leading to compounds 14a–b, 10a, 15 and 16

A solution of PhMgCl (2.0 M in THF, 14.7 mmol) was added to a mixture of (±)-**13** (1.00 g, 7.35 mmol) in hexane (100 mL) at rt under an argon atmosphere. Water (246 μL, 14.7 mmol) was added and the mixture was stirred for 10 min before another portion of PhMgCl (2.0 M in THF, 14.7 mmol) was added. Addition of water (246 μL, 14.7 mmol) followed by the addition of PhMgCl (2.0 M in THF, 14.7 mmol) was repeated for another two times. The resulting slurry was stirred at rt for 30 min whereafter aqueous saturated NH_4Cl (50 mL) was added. Stirring was continued for 10 min and the mixture was worked up as follows: the phases were separated and the water phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were dried (Na_2SO_4), filtered and the solvent was removed at reduced pressure. The residue was purified by column chromatography (SiO_2, heptane–EtOAc 90:10 to 33:67).

4.2.1. (±)-*endo*-5-Hydroxy-5-phenylbicyclo[2.2.2]oct-7-en-2-one 14a

Hydroxyketone **14a** (498 mg, 32%) was obtained as a transparent oil: TLC R_f = 0.52 (SiO_2, heptane–EtOAc 50:50); IR (NaCl) 3427, 1717 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.29–7.09 (m, 5H), 5.84–5.77 (m, 2H), 3.09–3.02 (m, 1H), 2.94 (dd, *J* = 18.1, 2.2 Hz, 1H), 2.74–2.71 (m, 1H), 2.11 (dd, *J* = 14.2, 3.4 Hz, 1H), 1.90 (dd, *J* = 14.2, 2.2 Hz, 1H), 1.81 (dd, *J* = 18.1, 3.1 Hz, 1H), 1.62 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.5, 149.4, 136.4, 129.5, 128.4, 127.5, 127.1, 76.0, 50.7, 46.3, 42.0, 35.9; HRMS (FAB+, direct inlet) [M+H] calcd for $C_{14}H_{15}O_2$: 215.1072; found 215.1074. $C_{14}H_{14}O_2$ requires C, 78.48; H, 6.59. Found: C, 78.40; H, 6.53.

4.2.2. (±)-*exo*-5-Hydroxy-5-phenylbicyclo[2.2.2]oct-7-en-2-one 14b

Hydroxyketone **14b** (278 mg, 18%) was obtained as a transparent oil: TLC R_f = 0.35 (SiO_2, heptane–EtOAc 50:50); IR (NaCl) 3435, 1728 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 7.40–7.32 (m, 2H), 7.14–7.00 (m, 3H), 6.12 (m, 1H), 5.95–5.86 (m, 1H), 3.02–2.94 (m, 1H), 2.67–2.60 (m, 1H), 2.40 (dd, *J* = 14.8, 2.1 Hz, 1H), 1.79 (dd, *J* = 18.7, 1.9 Hz, 1H), 1.64 (s, 1H), 1.50 (td, *J* = 18.9, 3.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.1, 145.4, 135.9, 130.2, 128.8, 127.9, 126.9, 77.2, 50.6, 47.0, 40.7, 35.5; HRMS (FAB+, direct inlet) [M+H] calcd for $C_{14}H_{14}O_2$: 214.0994; found 214.0993. Elementary analysis was not satisfactory due to partial product decomposition.

4.2.3. (±)-*endo*,*endo*-2,5-Diphenylbicyclo[2.2.2]oct-7-ene-2,5-diol 10a

Diol **10a** (123 mg, 6%) was obtained as a white solid: TLC R_f = 0.69 (SiO_2, heptane–EtOAc 50:50); mp 158–163 °C; IR (KBr) 3380 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.9 Hz, 4H), 7.36 (t, *J* = 7.9 Hz, 4H), 7.30–7.23 (m, 2H), 6.40 (dd, *J* = 4.4, 3.3 Hz, 2H), 3.29 (s, 2H), 3.06–2.98 (m, 2H), 2.61 (dd, *J* = 14.2, 3.2 Hz, 2H), 2.05 (dd, *J* = 14.2, 2.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.9, 134.8, 128.3, 127.0, 125.7, 75.5, 44.8, 41.9; HRMS (FAB+, direct inlet) [M] calcd for $C_{20}H_{20}O_2$: 292.1463; found 292.1457. $C_{18}H_{20}O_2$ requires C, 82.16; H, 6.89. Found: C, 82.16; H, 6.80.

4.2.4. (±)-*endo*,*exo*-2,5-Diphenylbicyclo[2.2.2]oct-7-ene-2,5-diol 15

Diol **15** (484 mg, 23%) was obtained as a white solid: TLC R_f = 0.58 (SiO_2, heptane–EtOAc 50:50); mp 177–181 °C; IR (KBr) 3497, 3425 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93–7.87 (m, 2H), 7.48–7.39 (m, 4H), 7.37–7.20 (m, 4H), 6.48–6.34 (m, 2H), 3.42 (dd, *J* = 14.5, 1.9 Hz, 1H), 3.08–2.97 (m, 2H), 2.18 (s, 1H), 2.15 (dd, *J* = 14.5, 3.8 Hz, 1H), 1.84 (s, 1H), 1.81 (dd, *J* = 14.5, 1.8 Hz, 1H), 1.67 (dd, *J* = 14.6, 3.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 144.8, 135.1, 132.4, 128.1, 128.0, 127.2, 127.1, 127.0, 126.5, 77.8, 76.2, 45.7, 44.4, 37.8, 37.7; HRMS (FAB+, direct inlet) [M] calcd for $C_{20}H_{20}O_2$: 292.1463; found 292.1454. $C_{20}H_{20}O_2$ requires C, 82.16; H, 6.89. Found: C, 82.27; H, 6.85.

4.2.5. (±)-*exo*,*exo*-2,5-Diphenylbicyclo[2.2.2]oct-7-ene-2,5-diol 16

Diol **16** (345 mg, 16%) was obtained as a white solid: TLC R_f = 0.19 (SiO_2, heptane–EtOAc 50:50); mp 193–197 °C; IR (KBr)

3356 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.26 (m, 10H), 6.74 (dd, J = 4.6, 3.2 Hz, 2H), 3.29 (m, 2H), 2.35 (dd, J = 14.8, 1.8 Hz, 2H), 2.11 (s, 2H), 1.65 (dd, J = 15.2, 3.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 134.4, 128.3, 127.6, 126.6, 77.1, 43.7, 37.7; HRMS (FAB+, direct inlet) [M] calcd for $C_{20}H_{20}O_2$: 292.1463; found 292.1459. $C_{20}H_{20}O_2$ requires C, 82.16; H, 6.89. Found: C, 82.28; H, 6.83.

4.3. General procedure for the reduction of acetophenone

Activated 4 Å molecular sieves (0.4 g) were added to a mixture of the ligand (0.1 mmol) in *t*BuOMe (1 mL) at rt under an argon atmosphere. The mixture was stirred for 2 h at rt and $Ti(OiPr)_4$ (0.1 mmol in 1 mL of *t*BuOMe) was added. The resulting mixture was heated at 45 °C for 90 min, cooled to rt and then acetophenone (1 mmol) was added. Stirring at rt was continued for 10 min before the mixture was cooled to −20 °C and catecholborane (1 M in THF, 1.5 mL) was added. The mixture was stirred at −20 °C for 24 h before the addition of satd NH_4Cl (5 mL). The cooling bath was removed and more satd NH_4Cl (5 mL), water (5 mL) and ether (10 mL) were added. The resulting mixture was stirred at rt for 60 min to ensure complete hydrolysis of the boronic esters and worked up as follows: the phases were separated and the water phase was extracted with ether (2 × 20 mL). The combined organic phases were washed with aqueous NaOH (1 M, 3 × 15 mL) and the combined water phases were back-extracted with ether (30 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed at reduced pressure. The residue was purified by column chromatography (SiO_2, pentane–ether 90:10) to give phenylethanol. The chemical structure was established by ^1H NMR spectroscopy and the ees were determined by HPLC (Chiralcel OD-H, hexane–*i*PrOH 90:10, 0.5 mL/min, UV detection at 254 nm): t = 12.7 min (*R*), t = 14.0 min (*S*).

4.4. (1*S*)-1-Phenyl-3-buten-1-ol

The homoallylic alcohol was prepared according to the literature procedure of Hall et al.[36] with benzaldehyde (35 mg, 0.33 mmol), $Sc(OTf)_3$ (16 mg, 0.03 mmol) and with allylborinate **18** (115 mg, 0.36 mmol) as the allylation reagent. The residue was purified by column chromatography (SiO_2, hexane:EtOAc 95:5) to give the title compound (29 mg, 59%) as a transparent oil: TLC R_f = 0.46 (SiO_2, heptane–EtOAc 67:33); HPLC (Chiralcel OD-H, hexane:iPrOH 97:3, 0.5 mL/min, UV detection at 210 nm): t_{minor}(*R*)=24.1 min, t_{major}(*S*)=26.3 min, 80% ee. ^1H NMR data were consistent with those reported.[39]

4.5. (1*S*,4*S*)-2,5-Di(naphthalen-1-yl)bicyclo[2.2.2]octa-2,5-diene 17

Molecular sieves (4 Å, 2 g) were added to a mixture of diol **7b** (110 mg, 0.28 mmol) in toluene (15 mL) at rt. The resulting mixture was stirred at 45 °C for 2 h and then cooled to ambient temperature. The mixture was filtered and the molecular sieves were rinsed with toluene (3 × 10 mL). The solvent was removed at reduced pressure and the residue was purified by column chromatography (SiO_2, heptane–EtOAc 1:1, TLC R_f = 0.74) to give **17** (49 mg, 49%) as a white solid (90% purity by ^1H NMR). An analytical sample of the mixture was further purified by preparative TLC (SiO_2, hexane–toluene 95:5) to give the diene **17** as a white solid: mp 65–67 °C; $[\alpha]_D$ = −198 (*c* 1.05, $CHCl_3$); IR (KBr) 3040, 2937, 2864, 797, 773 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 8.20 (dd, J = 8.1, 0.6 Hz, 2H), 7.71 (d, J = 7.8 Hz, 2H), 7.64 (d, J = 7.6 Hz, 2H), 7.39–7.22 (m, 8H), 6.53 (dd, J = 6.1, 1.9 Hz, 2H), 3.86 (dd, J = 6.0, 1.8 Hz, 2H), 1.63–1.53 (m, 2H), 1.52–1.43 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 148.9, 139.5, 134.9, 132.9, 132.6, 129.1, 128.4, 126.9, 126.5, 126.4, 126.1, 125.8, 44.8, 26.4; HRMS (FAB+, direct inlet) [M] calcd for $C_{28}H_{22}$: 358.1722; found 358.1733. $C_{28}H_{22}$ requires C, 93.81; H, 6.19. Found: C, 93.86; H, 6.24.

4.6. (1*R*,2*R*,4*S*,6*S*)-2,6-*O*-[allylboryl]-2-(Naphtalen-1-yl)-bicyclo[2.2.2]octanediol 18

A solution of allylmagnesiumbromide (1.0 M in ether, 3.52 mmol) was added to $B(OEt)_3$ (891 μL, 3.91 mmol) in ether (8 mL) at −78 °C under an argon atmosphere. The resulting slurry was stirred at −78 °C for 4 h and then added to a mixture of **3i** (900 mg, 3.36 mmol), ether (35 mL) and satd NH_4Cl (35 mL) at 0 °C. The resulting mixture was stirred at rt for 30 min and then worked up as follows: the phases were separated and the water phase was extracted with ether (3 × 35 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed at reduced pressure. The residue was purified by column chromatography (SiO_2 pre-treated with heptane–Et_3N 95:5, heptane–EtOAc 67:33, TLC R_f = 0.55) to give **18** (668 mg, 63%) as a transparent oil: ^1H NMR (400 MHz, C_6D_6) δ 8.80 (d, J = 8.4 Hz, 1H), 7.70 (dt, J = 8.2, 0.7 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.47–7.41 (m, 1H), 7.34–7.28 (m, 1H), 7.21 (dd, J = 7.4, 1.2 Hz, 1H), 7.18–7.13 (m, 1H), 6.20–6.07 (m, 1H), 5.13–5.05 (doublet of multiplets, 1H), 5.02–4.96 (doublet of multiplets, 1H), 4.06–4.00 (m, 1H), 2.31–2.21 (m, 2H), 2.14 (dt, J = 14.7, 2.7 Hz, 1H), 1.89 (d, J = 7.6 Hz, 2H), 1.88–1.79 (m, 1H), 1.69–1.58 (m, 1H), 1.46 (dq, J = 14.2, 2.8 Hz, 1H), 1.36 (heptet, J = 3.1 Hz, 1H), 1.06–0.95 (m, 1H), 0.87–0.71 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 141.8, 136.5, 136.3, 132.5, 129.7, 129.4, 128.8, 125.9, 125.9, 124.8, 123.1, 114.4, 76.1, 68.3, 47.4, 38.7, 35.8, 24.8, 23.4, 20.1; HRMS (FAB+, direct inlet) [M] calcd for $C_{21}H_{23}BO_2$: 318.1791; found 318.1784.

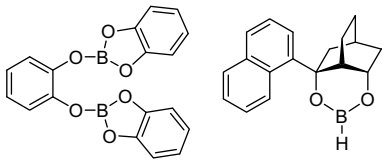
4.7. Synthesis of 20

BH_3·DMS (10.2 M, 0.11 mmol) was added to a mixture of **3i** (26.8 mg, 0.1 mmol) and toluene-d_8 (0.5 mL) in an NMR tube at 0 °C under an argon atmosphere. After 2 h at 0 °C a clear solution was obtained that was allowed to reach rt: ^1H NMR (400 MHz, toluene-d_8) δ 8.68 (d, J = 8.6 Hz, 1H), 7.66 (dd, J = 8.1, 1.1 Hz, 1H), 7.56 (dd, J = 6.1, 2.9 Hz, 1H), 7.41–7.34 (m, 1H), 7.32–7.26 (m, 1H), 7.18–7.13 (m, 2H), 5.50–3.75 (v br s, 1H), 3.98 (dt, J = 10.0, 3.0 Hz, 1H), 2.28 (dt, J = 14.7, 2.9 Hz, 1H), 2.19 (q, J = 3.2 Hz, 1H), 2.12–2.04 (m, 1H), 1.86 (ddt, J = 17.0, 9.8, 2.7 Hz, 1H), 1.74–1.64 (m, 1H), 1.45 (dq, J = 14.3, 2.9 Hz, 1H), 1.36 (heptet, J = 3.1 Hz, 1H), 1.11–1.00 (m, 1H), 0.92–0.81 (m, 1H), 0.80–0.69 (m, 1H); ^{13}C NMR (100 MHz, toluene-d_8) δ 141.7, 136.3, 132.4, 129.7, 129.5, 128.8, 125.9, 125.9, 124.7, 123.0, 76.0, 68.1, 47.8, 38.8, 36.1, 24.9, 23.5, 20.4; ^{11}B NMR (relative to BH_3·DMS (−20.2 ppm), 160 MHz, toluene-d_8) δ +24.4 (d); MS (FAB+, direct inlet) m/z 278 [M].

4.8. Discussion regarding the catecholborane quality

Initially, results comparable to those obtained with a good solution of CBH in THF were obtained when using CBH solutions in toluene and with toluene as the only solvent for the reaction. However, after employing several different solutions of CBH in toluene, we soon realized that the results were still not reproducible. Checking the quality of the CBH solutions by ^{11}B NMR was not informative enough since all solutions tested showed similar spectra with approximately the same relative amounts of impurities, despite the different ees obtained in the reductions. Moreover, the comparatively good CBH/THF solution used for the testing of the ligands in the reduction of acetophenone was revealed by ^{11}B NMR to contain a larger amount of impurities as compared to the toluene solutions. Attempts were made to identify the source of the problem. Commercially available CBH solutions are known to contain considerable amounts of borate

impurities (15–20%), predominantly the tri-*O*-phenylene bis-borate **19** (Fig. 10).[40]



19 **20**

Figure 10.

Since the ^{11}B NMR spectra showed that borate **19** was the major impurity in our CBH solutions, it was added to the reaction mixtures (up to 30 mol %) prior to the addition of the CBH solution. However, borate **19** did not interfere with the reaction. The ees of the reduction products were similar as for the control experiment. The ees obtained when using five different CBH solutions (A–E) in toluene as reagent for the reductions are presented in Table 5.

Table 5
Variation in ee for the reduction of acetophenone with anisyl-BODOL **4a** in the presence of Ti(O*i*Pr)$_4$ using different solutions of CBH[a]

Entry	CBH-solution[b]	Additive	ee (%)[c]
1	A[d]	—	78
2	B[e]	—	72
3	C[f]	—	82
4	C[f]	Catechol (30 mol %)[g]	83
5	C[f]	Acetone (30 mol %)[g]	90
6	C[f]	$NaBH_4$ (5 mol %)[g]	87
7	D[f]	—	70
8	D[f]	—[h]	93
9	D[f]	DMS (10 mol %)[i]	79
10	D[f]	BH_3·DMS (10 mol %)[j]	62
11	E[f]	—	71
12	E[f]	DMS (30% of total solvent volume)[i]	96
13	E[f]	*t*BuOMe (30% of total solvent volume)[i]	97

[a] The complexes were prepared by the addition of Ti(O*i*Pr)$_4$ to the ligand in a toluene solution containing 4 Å molecular sieves, followed by stirring for 90 min at 45 °C.[41]
[b] Different batches of 1 M CBH in toluene (A–E).
[c] Determined by HPLC on Chiralcel OD-H.
[d] 1 M solution in toluene prepared by dilution of commercial CBH (98%).
[e] Prepared by the method of Brown et al.[40]
[f] Commercial solution of CBH (1 M).
[g] Added to the solution of CBH before addition to the reaction mixture.
[h] Preparation of the Ti-**4a** complex in DMS.
[i] Added at −20 °C before addition of CBH.
[j] Added after addition of CBH.

Neither neat (entry 1) nor freshly prepared (entry 2) CBH solution gave significantly different results as compared to the commercial solutions (entries 3, 7 and 11). Addition of catechol prior to the addition of the CBH solution did not affect the ee (entry 4). Although we could not identify any particular impurity in the CBH solutions that caused the varying ees, it was found that the ees were improved by pre-treatment of the CBH solutions with acetone (entry 5), $NaBH_4$ (entry 6) or by the addition of a polar solvent component, DMS or *t*BuOMe (entries 8, 9 and 12, 13).

The increase in ee observed when pre-treating the CBH solution with acetone may partially be due to removal of the small amounts of free borane present in the CBH solution by reduction of acetone to isopropanol. Addition of BH_3·DMS (entry 10) resulted in an almost proportional decrease in ee. It is known that BH_3 to some extent is formed by disproportionation of CBH and Ti(O*i*Pr)$_4$ and the drop in ee observed in the reductions with some CBH solutions may be caused by formation of BH_3 in the reaction mixtures. An ether solvent may have a stabilizing effect on the catalytically active complex which possibly could prevent disproportionation of CBH and Ti(O*i*Pr)$_4$ to BH_3. However, this does not explain the drop in ee observed for some of the CBH solutions in THF.

Addition of 1 equiv BH_3·DMS to ligand **3i** at 0 °C in toluene resulted in complete formation of the cyclic borane **20** (Fig. 10) after 2 h. To investigate if the borane **20** possibly could function as a reducing agent, reduction of acetophenone at −20 °C for 24 h using an equimolar amount of **20**, both with and without Ti(O*i*Pr)$_4$, was attempted. No product was observed in the reaction where Ti(O*i*Pr)$_4$ was excluded and only traces of phenylethanol was observed when 1 equiv of Ti(O*i*Pr)$_4$ was used. Thus, borane **20** could be excluded as the hydride source in the CBH reductions.

Finally, the titanium complex of **4a** together with 1 or 2 equiv of CBH (1M in THF) was studied by ^{1}H NMR. Since none of the initially formed Ti-**4a** complex was apparent in the resulting spectrum it is plausible that a borate is formed between the ligand and CBH. A well-defined spectrum was not obtained either with 1 or 2 equiv of CBH added. This observation is somewhat puzzling since the maturation period of the initially formed catalyst has been found to affect the ee of the products.[22] Thus, further investigation is required to give insight into the nature of the catalytically active complex in this mixture as well as in the detailed mechanism.

5. Computations

The PM3 calculations were performed on a Silicon Graphics O_2 work station with R-10000 processor using the SPARTAN 5.0.3 program.[28]

5.1. X-ray structural analysis of compound 8a

Intensity data were collected at 293 K with a Bruker Smart CCD system using ω scans and a rotating anode with Mo Kα radiation (λ = 0.71073 Å).[42] The intensity was corrected for Lorentz and polarization effects using SADABS.[43] The first 50 frames were collected again at the end to check for decay. No decay was observed. All reflections were merged and integrated using SAINT.[44] The structure was solved by direct methods and refined by full matrix least-square calculations on F^2 using SHELXTL5.1.[45] The hydrogen atoms were constrained to parent sites, using a riding model. The crystal was a weak scatterer giving rise to a large fraction of weak reflections (73% with $I < 2\sigma(I)$) and thus a large R_{int}.[46] CCDC No: 695636.

5.1.1. Crystal data and collection and refinement details

$C_{20}H_{20}O_2$, M = 292.36, orthorhombic, a = 7.1566(3), b = 18.6088(9), c = 22.8434(10) Å, V = 3042.2(2) Å^3, space group $P2_12_12_1$ (No. 19), Z = 8, μ = 0.081 mm^{-1}, 31,718 reflections measured, 5473 unique (R_{int} = 0.229) which were used in all calculations. The final $wR(F^2)$ was 0.0733 and the S value 0.951 (all data). The $R(F)$ was 0.0548 ($I > 2\sigma(I)$).

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References

1. Yates, P.; Burnell, D. J.; Freer, V. J.; Sawyer, J. F. *Can. J. Chem.* **1987**, *65*, 69–77.

2. Martin, S. F.; Assercq, J. M.; Austin, R. E.; Dantanarayana, A. P.; Fishpaugh, J. R.; Gluchowski, C.; Guinn, D. E.; Hartmann, M.; Tanaka, T.; Wagner, R.; White, J. B. *Tetrahedron* **1995**, *51*, 3455–3482.
3. Moore, S. Dissertation, Georgia Institute of Technology, 2004.
4. Seebacher, W.; Berger, H.; Kaiser, M.; Brun, R.; Saf, R.; Weis, R. *Monatsh. Chem.* **2006**, *137*, 471–482.
5. Otomaru, Y.; Okamoto, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 2503–2508.
6. Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584–13585.
7. Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628–1629.
8. Consiglio, G.; Nefkens, S. C. A. *Tetrahedron: Asymmetry* **1990**, *1*, 417–420.
9. Castellanos-Paez, A.; Castillon, S.; Claver, C. *J. Organomet. Chem.* **1997**, *539*, 1–7.
10. Finet, L.; Dakir, M.; Castellote, I.; Kaoudi, T.; Toupet, L.; Arseniyadis, S. *Eur. J. Org. Chem.* **2007**, 335–341.
11. Lindsley, C. W.; DiMare, M. *Tetrahedron Lett.* **1994**, *35*, 5141–5144.
12. Giffels, G.; Dreisbach, C.; Kragl, U.; Weigerding, M.; Waldmann, H.; Wandrey, C. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2005–2006.
13. Huang, W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1998**, *63*, 1364–1365.
14. Fu, I. P.; Uang, B. J. *Tetrahedron: Asymmetry* **2001**, *12*, 45–48.
15. Ford, A.; Woodward, S. *Angew. Chem., Int. Ed.* **1999**, *38*, 335–336.
16. Blake, A. J.; Cunningham, A.; Ford, A.; Teat, S. J.; Woodward, S. *Chem. Eur. J.* **2000**, *6*, 3586–3594.
17. Huang, W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 7940–7956.
18. Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 92–138.
19. Naraku, G.; Hori, K.; Ito, Y. N.; Katsuki, T. *Tetrahedron Lett.* **1997**, *38*, 8231–8232.
20. Gardiner, J. M.; Crewe, P. D.; Smith, G. E.; Veal, K. T. *Chem. Commun.* **2003**, 618–619.
21. Almqvist, F.; Torstensson, L.; Gudmundsson, A.; Frejd, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 376–377.
22. Sarvary, I.; Almqvist, F.; Frejd, T. *Chem. Eur. J.* **2001**, *7*, 2158–2166.
23. Sarvary, I.; Norrby, P.-O.; Frejd, T. *Chem. Eur. J.* **2004**, *10*, 182–189.
24. Sarvary, I.; Wan, Y.; Frejd, T. *J. Chem. Soc., Perkin Trans. 1* **2002**, 645–651.
25. Mori, K.; Nagano, E. *Biocatalysis* **1990**, *3*, 25–36.
26. Almqvist, F.; Eklund, L.; Frejd, T. *Synth. Commun.* **1993**, *23*, 1499–1505.
27. Botes, A. L.; Harvig, D.; van Dyk, M. S.; Sarvary, I.; Frejd, T.; Katz, M.; Hahn-Haegerdal, B.; Gorwa-Grauslund, M. F. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1111–1114.
28. SPARTAN, version 5.0.3, Hehre, W. J.; Burke, L. D.; Shusterman A. J.; Pietro, W. J., Wavefunctions, 18401 Von Karman, Suite 370, Irvine, California 92715.
29. Friberg, A.; Johanson, T.; Franzen, J.; Gorwa-Grauslund, M. F.; Frejd, T. *Org. Biomol. Chem.* **2006**, *4*, 2304–2312.
30. Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625–1627.
31. Lightner, D. A.; Paquette, L. A.; Chayangkoon, P.; Lin, H. S.; Peterson, J. R. *J. Org. Chem.* **1988**, *53*, 1969–1973.
32. DIAMOND, Brandenburg, K., Program for Molecular Graphics; Crystal Impact, Bonn, Germany, 2000.
33. Shintani, R.; Okamoto, K.; Otomaru, Y.; Ueyama, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 54–55.
34. Shintani, R.; Sannohe, Y.; Tsuji, T.; Hayashi, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 7277–7280.
35. Soergel, S.; Tokunaga, N.; Sasaki, K.; Okamoto, K.; Hayashi, T. *Org. Lett.* **2008**, *10*, 589–592.
36. Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 10160–10161.
37. Widegren, M.; Dietz, M.; Friberg, A.; Frejd, T.; Hahn-Hägerdal, B.; Gorwa-Grauslund, M. F.; Katz, M. *Synthesis* **2006**, *3527–3530.*
38. Ikai, K.; Takeuchi, K.; Kinoshita, T.; Haga, K.; Komatsu, K.; Okamoto, K. *J. Org. Chem.* **1991**, *56*, 1052–1058.
39. Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59*, 6620–6628.
40. Kanth, J. V. B.; Periasamy, M.; Brown, H. C. *Org. Process Res. Dev.* **2000**, *4*, 550–553.
41. Sarvary, I. Doctoral Thesis, Lund University, 2002.
42. BrukerAXS, SMART, Area Detector Control Software, Bruker Analytical X-ray System, Madison, Wisconsin, USA, 1995.
43. Sheldrick, G. M. SADABS, *Program for Absorption Correction*; University of Göttingen: Germany, 1996.
44. BrukerAXS, SAINT, Integration Software, Bruker Analytical X-ray System, Madison, Wisconsin, USA, 1995.
45. Sheldrick, G. M. SHELXTL*5.1, Program for Structure Solution and Least Square Refinement*; University of Göttingen: Germany, 1998.
46. Weiss, M. S.; Hilgenfeld, R. *J. Appl. Crystallogr.* **1997**, *30*, 203–205.