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Cleft molecules as organocatalysts in an asymmetric hetero-Diels–Alder reaction

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Abstract—The synthesis and application of chiral carbocyclic cleft molecules derived from 2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene-4,8-dione in the hetero-Diels–Alder reaction of benzaldehydes and aminodiene **14** is presented. Catalysis by single hydrogen-bond activation gave up to 52% ee.

1. Introduction

Chiral diols and diphenols, such as TADDOLs and BINOLs, are frequently used ligands in asymmetric transformations.[1,2] In 2003, Rawal et al. reported the first successful application of chiral diols as enantioselective hydrogen-bonding (H-bonding) organocatalysts in which TADDOL derivatives efficiently catalyzed asymmetric hetero-Diels–Alder reactions of aminodienes and aldehydes.[3] The TADDOLs have been employed as H-bonding organocatalysts in other asymmetric cycloaddition reactions,[4,5] in asymmetric *N*-nitroso aldol reactions of enamines[6] and in enantioselective, vinylogous Mukaiyama aldol reactions.[7] Examples of other chiral diols functioning as H-bonding organocatalysts, for example, BINOL- and BAMOL (1,1′-biaryl-2,2′-dimethanol)-derivatives, have also been reported.[8–10] Crystallographic studies show that the TADDOL and BAMOL establish an intramolecular H-bond between the two hydroxy groups.[4,11] Computational investigations of the mode of activation by TADDOL in the asymmetric hetero-Diels–Alder and the Diels–Alder reaction confirm that cooperative catalysis is favourable (**B**, Fig. 1).[12–14] The H-bonding feature of the BINOL derivatives is more uncertain. However, in the Morita–Bayliss–Hillman reaction, the involvement of both hydroxy groups for catalysis was evident by a decrease in enantioselectivity and yield when one of the hydroxy groups was methylated.[15] Although there is a possibility that the BINOLs act through double H-bond activation (**C**), intramolecular H-bonding increases the acidity of the remaining O–H bond and cooperative catalysis (**B**) is more likely. Organization of the catalyst–substrate complex by the intramolecular H-bond is most likely important for a highly enantioselective reaction. As a consequence of this, highly enantioselective transformations by single H-bond donation (**A**) remain a challenge. To the best of our knowledge, no examples of successful nonracemic monodentate alcohol catalysts have been reported.

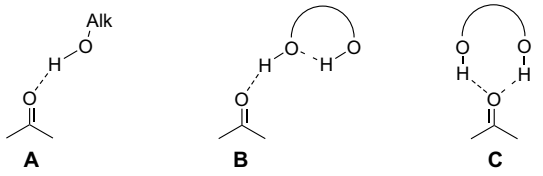

Figure 1. Three modes of carbonyl activation by H-bonding: (A) single H-bond activation, (B) single H-bond activation enhanced by intramolecular H-bonding, (cooperative catalysis) (C) double H-bond activation.

Herein we report the synthesis and application of chiral carbocyclic cleft molecules as H-bonding catalysts. These cleft like structures are reminiscent of Tröger's base **1a** (Fig. 2), previously used in host–guest studies for the positioning of functional groups in a predictable geometry.[16–18] The possibility of utilizing a chiral cleft for substrate-organization in combination with hydrogen-bond activation for enantioselective catalysis was investigated, as well as

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enantioselectivity originating from H-bonding by simple mono-alcohols.

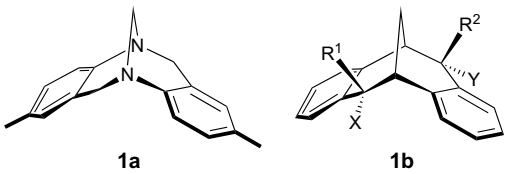
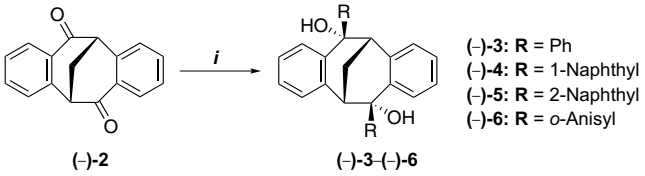


Figure 2. Tröger's base **1a** and general structure of the synthesized analogs **1b**.

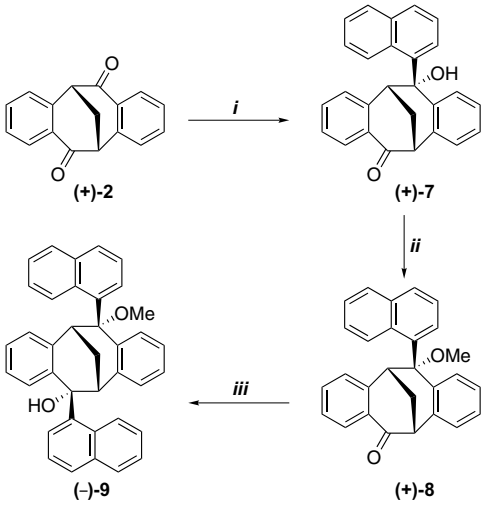
2. Results and discussion

2.1. Synthesis of the catalysts

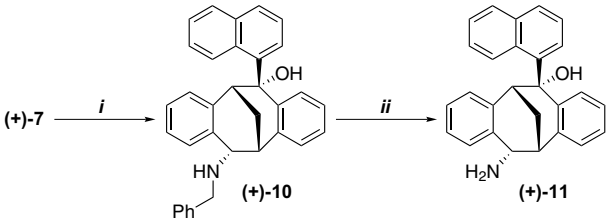
The C_2-symmetric diols (−)-**3**–(−)-**6** were synthesized from diketone (−)-**2**[19,20] by the addition of an excess of the corresponding Grignard- or lithium reagents (Scheme 1), while the hydroxyketone (+)-**7** (Scheme 2) was obtained in high yield by addition of 1.2 equiv of 1-naphthylMgBr. Compound (−)-**9** was obtained by methylation of (+)-**7** followed by the addition of the second naphthyl substituent. Amino alcohol (+)-**10** (Scheme 3) was synthesized via formation of the corresponding benzylimine derivative, followed by the reduction with $NaBH_4$ in MeOH (52% overall yield).



Scheme 1. Reagents: (i) RMgX or *o*-AnLi in THF.



Scheme 2. Reagents and conditions: (i) 1-naphthylMgBr, THF, rt, 1 h, 88%; (ii) MeI, NaH, THF, 0 °C, 98%; (iii) 1-naphthylMgBr, THF, rt, 5 h, 54%.



Scheme 3. Reagents and conditions: (i) (a) $BnNH_2$, 4 Å MS, toluene, reflux, 22 h: (b) $NaBH_4$, MeOH, reflux, 5 h, 52%; (ii) Pd/C (5%), HCOOH, MeOH, rt, 5 h, 90%.

To improve the yield, the imine reduction was attempted with $LiAlH_4$, but no conversion of the intermediate imine was observed. Hydrogenolysis of (+)-**10** was problematic. Catalytic hydrogenation using Pd/C and molecular hydrogen resulted in irreproducible yields due to hydrogenolysis of the formed compound (+)-**11** during the course of the reaction. This was circumvented by the use of formic acid and Pd/C in a transfer hydrogenation,[21] which resulted in a high yield of (+)-**11** (90%). The previously synthesized amines (+)-**12** and (−)-**13**[19] were also included in the present investigation (Fig. 3).

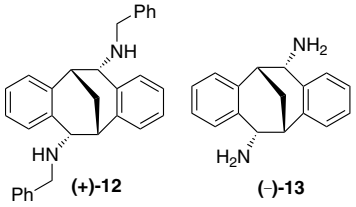
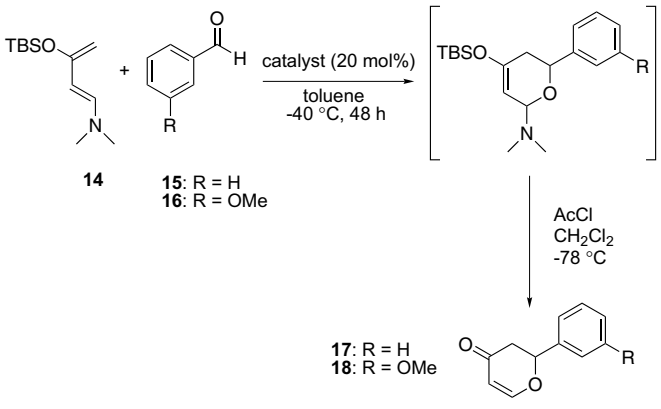


Figure 3.

2.2. Catalysis

The hetero Diels–Alder reaction of benzaldehyde and diene **14** was chosen as the test reaction for the organocatalytic study (Scheme 4).[3] The reactions were performed at −40 °C in toluene for 48 h.[†] At this temperature, the back-



Scheme 4.

[†] A decrease of the reaction temperature to −78 °C resulted in a higher ee (61% of **17** with ligand (−)-**4**), but much lower yield (<3%). No improvement was noticed by using CH_2Cl_2 or hexane as solvents.

ground reaction was negligible. Treatment of the Diels–Alder adduct with acetyl chloride resulted in the desired dihydro-4-pyrone. Initially, diols (−)-**3**–(−)-**6** were tested for organocatalytic activity with varied results (Table 1, entries 3–6). The phenyl- and 1-naphthyl substituted diols (−)-**3** and (−)-**4** gave similar results while the 2-naphthyl substituted diol (−)-**5** caused a lower ee and yield (entry 5). The anisyl substituted diol (−)-**6** catalyzed the reaction but failed to induce enantioselectivity. *m*-Methoxybenzaldehyde was also used as dienophile with diols (−)-**3** and (−)-**4**, with similar results as for benzaldehyde (entries 14 and 15). Since the best result was obtained with 1-naphthyl substituted diol (−)-**4** (entry 4), the 1-naphthyl group was chosen as the substituent for further catalyst modification.

Table 1. Application of compounds **1**–**13** in the hetero Diels–Alder reaction between aminodiene **14** and benzaldehydes **15** or **16**

Entry	Catalyst	Substrate	Product	ee[a]	Configuration[b]	Yield[d] (%)
1	(+)-**1a**	**15**	**17**	0	—	20
2	(+)-**2**	**15**	**17**	0	—	14
3	(−)-**3**	**15**	**17**	38	(*S*)	41
4	(−)-**4**	**15**	**17**	48	(*S*)	50
5	(−)-**5**	**15**	**17**	10	(*S*)	9
6	(−)-**6**	**15**	**17**	0	—	24
7	(+)-**7**	**15**	**17**	52	(*R*)	41
8	(+)-**8**	**15**	—	0	—	0
9	(−)-**9**	**15**	**17**	50	(*R*)	40
10	(+)-**10**	**15**	**17**	14	(*R*)	36
11	(+)-**11**	**15**	**17**	38	(*R*)	29
12	(+)-**12**	**15**	**17**	0	—	7
13	(−)-**13**	**15**	**17**	0	—	21
14	(−)-**3**	**16**	**18**	44	(*S*)[c]	59
15	(−)-**4**	**16**	**18**	50	(*S*)[c]	42

[a] Determined by HPLC analysis on a Chiralcel OD-H column.
[b] Determined by order of elution on the Chiralcel OD-H column.
[c] Assumed configuration by order of elution on the Chiralcel OD-H column as compared to elution order of 2-phenyl-2,3-dihydro-pyran-4-on.
[d] Isolated yields.

Catalysis by inclusion in the cleft was investigated via the application of diketone (+)-**2** and Tröger's base (+)-**1a** in the reaction. Although the yields were low [(+)-**1a**, 20% and (+)-**2**, 14%] a significant amount of product was isolated for both catalysts. This showed that hydrogen-bonding was not an absolute requirement and the cleft itself had an unexpected catalytic effect, although the enantioselectivities were lost (entries 1 and 2).

Due to the long distance between the two hydroxy groups in the diols, it is questionable if both hydroxyl groups are involved in catalysis. Although intramolecular cooperative H-bonding (**B**, Fig. 1) is not viable, activation of the carbonyl by double H-bond activation (**C**) could not be excluded. Compound (+)-**8**, with no ability of H-bond donation, was tested in the reaction but had no catalytic effect (entry 8). However, the monodentate alcohols (+)-**7** and (−)-**9** afforded yields and enantioselectivities that essentially did not differ from the results obtained for diol (−)-**4**. Thus, catalysis most likely occurs by single H-bond activation (**A**, Fig. 1). The total loss of catalytic effect for compound (+)-**8** was somewhat surprising in view of the results obtained with compounds (+)-**1a** and (+)-**2** but may be due to steric effects of the methoxy group preventing the reactants to be accommodated in the cleft. Also surprising was the lack of ee in the application of (−)-**6**. There was a catalytic effect, but the coordination of benzaldehyde apparently exposed its *re*- and *si*-face equally to the diene. This problem might be due to intramolecular H-bonding with the methoxy oxygen, which disturbs H-bond donation to the substrate aldehyde.

Inclusion complexes of hydroxyketone **19** (Fig. 4) with acetone[20] and DMSO[22] have been reported. The crystal structure of DMSO and **19** showed an H-bond between the sulfoxide oxygen and the hydroxyl, which allowed the DMSO sulfur atom to be placed almost central in the cleft. We can therefore speculate that a similar positioning of the benzaldehyde, to achieve a suitably rigid catalyst–substrate complex, is possible.

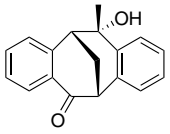


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Figure 4.

As a result we undertook a molecular mechanics computational investigation in the present case. Thus, by using MACROMODEL v.6.5,[23] benzaldehyde was placed in the cavity of (+)-**7** and the complex was then energy minimized by the procedure described in Section 4. Three low energy arrangements were found, *R*1, *R*2 and *S*, (Fig. 5) having steric energies 234.34, 236.11 and 236.08 kJ/mol, respectively. The population distribution at −40 °C calculated by the Boltzman factor corresponds to 55% ee of the product if we assume that the attachment of the diene can only occur from the exposed face of the carbonyl, that is, the *re*-face of *R*1 and *R*2 and the *si*-face of S. The ee compares well with the experimental value of 52% ee. Thus it is possible that the benzaldehyde behaves similar to DMSO in coordinating to the cavity of compounds such as **7** and **19**. Although the computations using benzaldehyde and ketoalcohol **7** seem to fit the experimental values of the ee rather well, it is doubtful that the other catalysts will coordinate the benzaldehyde in the same manner. Our interpretation is rather that there are several different modes of coordination depending on the exact structure of the catalyst.

Hydrogen-bonding solvents greatly accelerate hetero Diels–Alder reactions.[24] Thus, we also performed a hetero Diels–Alder reaction with isopropanol as a catalyst (20 mol %). The yield obtained (39%) was in the same range as for the best performing cleft molecule catalysts. Next, a selection of chiral monodentate alcohols (Fig. 6) was tested as catalysts in the reaction of diene **14** with benzaldehyde (Table 2). Among these alcohols, only the bicyclic hydroxy ketone (−)-**22** gave a notable ee of 28% (entry 3).

Diamines (+)-**12** and (−)-**13** gave disappointing results in terms of both yields and ees (entries 12 and 13). These

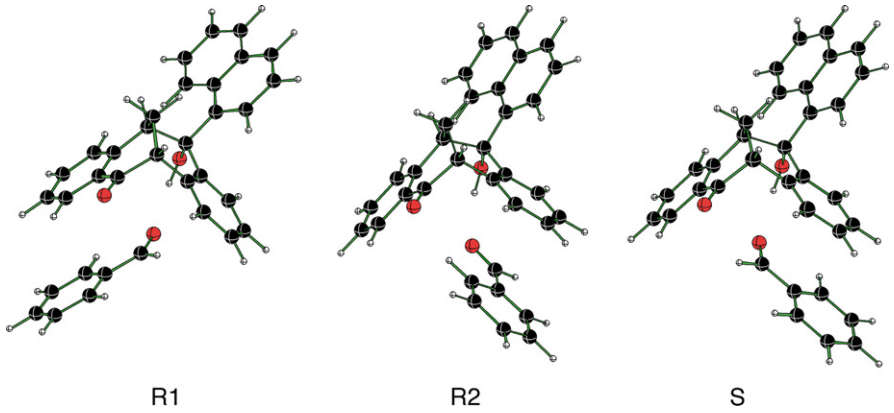

Figure 5.

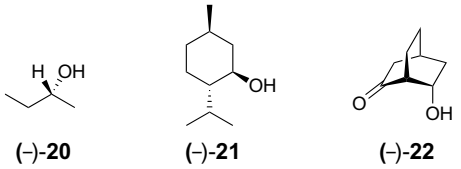

Figure 6.

Table 2. Application of alcohols **20**–**22** in the hetero Diels–Alder reaction between diene **14** and benzaldehyde

Entry	Catalyst	ee[a]	Configuration[b]	Yield[c] (%)
1	(–)-**20**	0	—	38
2	(–)-**21**	8	(*S*)	47
3	(–)-**22**	28	(*S*)	48

[a] Determined by HPLC analysis on a Chiralcel OD-H column.
[b] Determined by order of elution on a Chiralcel OD-H column.
[c] Isolated yields.

results showed that amine H-bonding was not efficient in this system. Aminoalcohol (+)-**11** showed slightly lower enantioselectivity when compared to the corresponding diol (−)-**4**, while the incorporation of a benzyl group gave inferior results [(+)-**10**, entry 10].

3. Conclusion

A novel chiral organocatalyst system based on the dibenzobicyclo[3.3.1]nona-2,6-diene framework has been presented. Up to 52% ee was obtained in a hetero Diels–Alder reaction between benzaldehydes **15** or **16** and diene **14**. These cleft like compounds are known for the recognition of substrates in the cleft[20,22] and despite the modest enantioselectivities obtained, other substrates than benzaldehyde derivatives may fit better in the cavities of the catalysts. Transition state structure organization could be envisaged by coordination of the substrate in the cleft in combination with a H-bond for enantioselective catalysis. The structure of the cleft can be changed by substituents on the aryl rings,[25] which could be used for tailoring the system for the recognition of specific substrates. Although the performances of the aminoalcohol derivatives in this reaction were inferior, they may be useful in organocatalytic enamine-type reactions. Thus, this ligand motif may be useful for other organocatalytic reactions.

4. Experimental

4.1. General methods

Anhydrous THF was purchased from Aldrich. Tröger's base was purchased from Fluka. PhMgCl (2.0 M in THF), 2-naphthylMgBr (0.5 M in THF), (*R*)-(−)-2-butanol, (−)-**20** and (1*R*,2*S*,5*R*)-(−)-menthol, (−)-**21**, were purchased from Aldrich. 6-Hydroxy-bicyclo[2.2.2]octan-2-one, (−)-**22**, was synthesized according to literature methods.[26,27] Column chromatography was performed on Matrex (25–70 μm) silica gel or pre-packed Isolute 10 g SiO_2. TLC was carried out on silica gel (60 F_{254}, Merck). 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. NMR spectra were recorded on a Bruker DRX 400 MHz spectrometer using the residual solvent as internal standard. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter at 20 °C and are given in 10^{-1} deg cm^2 g^{-1}. IR was recorded on a Shimadzu 8300 FTIR spectrometer. Melting points were taken on a Sanyo Gallenkamp melting point apparatus (MPD.350.BM3.5) and are uncorrected. Elemental analyses were performed by H. Kolbe Mikroanalytisches Laboratorium. HPLC analyses were performed on a Chiralcel OD-H column (250 × 4.6 id, 5 μm) (Daicel) on a Varian Prostar system equipped with a PDA detector. Flow rate: 0.5 mL min^{-1}, detection at 254 nm. Retention times using hexane–2-propanol 90:10 were: 12.4 min [(−)-**2**], 19.1 min [(+)-**2**], 26.6 min ((2*S*)-phenyl-2,3-dihydro-pyran-4-one), 28.7 min ((2*R*)-phenyl-2,3-dihydro-pyran-4-one), 39.9 min ((+)-(3-methoxy-phenyl)-2,3-dihydro-pyran-4-one) and 56.3 min ((−)-(3-methoxy-phenyl)-2,3-dihydro-pyran-4-one).

4.2. General procedure for the synthesis of 3–6

The corresponding Grignard- or organolithium reagent was added dropwise to a solution of **2**[19,20] (1.2 mmol, 0.3 g) in dry THF (5 mL) at rt under an argon atmosphere.

The resulting mixture was stirred at rt for 2 h whereafter aqueous satd NH_4Cl (3 mL) was added. The aqueous phase was extracted with ethyl acetate (3×10 mL), the combined organic phases washed with aqueous satd $NaHCO_3$ and dried over Na_2SO_4. The solvent was removed at a reduced pressure and the resulting residue purified by column chromatography on silica to give the product that could be further purified by recrystallization from ethanol.

4.2.1. (−)-(1*S*,4*S*,5*S*,8*S*)-4,8-Diphenyl-2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene-4,8-diol (−)-3. The title compound was synthesized following the general procedure, from (−)-**2** (0.3 g, 1.2 mmol) and 2.0 M PhMgCl in THF (1.8 mL, 3.6 mmol). The residue was purified by column chromatography (SiO_2, heptane–EtOAc 80:20) to give (−)-**3** (0.25 g, 90%) in >99% ee as a white solid: TLC R_f 0.41 (heptane–EtOAc 70:30); mp 218 –219 °C (from EtOH); $[\alpha]_D^{20} = -75$ (*c* 1.3, $CHCl_3$); IR (KBr) 3551 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.08 (2H, t, $J = 3.3$ Hz), 2.22 (2H, br s), 3.29 (2H, t, $J = 3.3$ Hz), 7.17–7.20 (4H, m), 7.23–7.26 (4H, m), 7.27–7.33 (4H, m), 7.38 (2H, td, $J = 7.4$, 1.6 Hz), 7.44 (2H, dd, $J = 7.7$, 1.5 Hz), 7.62 (2H, dd, $J = 7.6$, 1.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 46.8, 78.7, 127.3, 127.8, 127.8, 127.8, 128.6, 130.1, 131.1, 135.9, 141.8, 148.5; HRMS (FAB+, direct inlet) [M]: calcd for $C_{29}H_{24}NaO_2$: 427.1674. Found: 427.1678 (Found: C, 86.20; H, 5.93. $C_{29}H_{24}O_2$ requires C, 86.11; H, 5.98).

4.2.2. (−)-(1*S*,4*R*,5*S*,8*R*)-4,8-Di(1-naphthyl)-2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene-4,8-diol (−)-4. The title compound was synthesized following the general procedure, from (−)-**2** (0.93 g, 3.74 mmol) and 1.0 M 1-naphthylMgBr in THF (10 mL, 10 mmol, added in two equal portions). The residue was purified by column chromatography (SiO_2, pentane–diethyl ether 80:20) to give (−)-**4** (1.00 g, 98%) in >99% ee as a white solid: TLC heptane–EtOAc 90:10, R_f 0.37; mp 208–211 °C (from EtOH); $[\alpha]_D^{20} = -101$ (*c* 1.00, $CHCl_3$); IR (KBr) 3546 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.92 (2H, t, $J = 3.1$ Hz), 2.44 (2H, s), 4.05 (2H, t, $J = 3$ Hz), 6.35 (2H, d, $J = 7.3$ Hz), 7.11 (2H, t, $J = 7.9$ Hz), 7.37–7.42 (2H, m), 7.49–7.54 (4H, m), 7.62–7.72 (6H, m), 7.87 (2H, d, $J = 8.13$ Hz), 7.96 (2H, d, $J = 7.6$ Hz), 9.47 (2H, d, $J = 8.7$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.3, 42.2, 81.7, 124.2, 125.5, 125.8, 127.6, 127.9, 128.7, 129.3, 129.5, 129.8, 130.5, 131.3, 131.5, 135.2, 136.2, 142.1, 143.5; HRMS (FAB+, direct inlet) [M]: calcd for $C_{37}H_{28}NaO_2$: 527.1987. Found: 527.1990 (Found: C, 87.96; H, 5.64. $C_{37}H_{28}O_2$ requires C, 88.07; H, 5.59).

4.2.3. (−)-(1*S*,4*S*,5*S*,8*S*)-4,8-Di(2-naphthyl)-2,3:6,7dibenzobicyclo[3.3.1]nona-2,6-diene-4,8-diol (−)-5. The title compound was synthesized following the general procedure, from (–)-**2** (1.00 g, 4.03 mmol) and 2-naphthylMgBr (0.5 M in THF, 10 mL, 5 mmol). The residue was purified by column chromatography (SiO_2, heptane–EtOAc 90:10) to give (–)-**5** (1.89 g, 93%) in >99% ee: TLC R_f 0.28 (heptane–EtOAc 90:10,); mp 308–310 °C (from EtOAc–toluene); $[\alpha]_D^{20} = -228$ (*c* 1.07, $CHCl_3$); IR (KBr) 3531, 3484 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.13 (2H, t, $J = 3.2$ Hz), 2.35 (2H, br s), 3.45 (2H, t, $J = 3.1$ Hz), 7.30 (2H, d, $J = 1.4$ Hz), 7.36 (2H, td, $J = 7.5$, $J = 1.3$ Hz), 7.42–7.48 (6H, m), 7.52 (2H, dd, $J = 7.7$, $J = 1.3$ Hz), 7.66–7.69 (4H, m), 7.75 (2H, dd, $J = 7.6$, 1.1 Hz), 7.81–7.84 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.7, 46.5, 78.9, 125.5, 126.2, 126.2, 127.4, 127.6, 127.7, 127.9, 128.5, 128.8, 130.3, 131.2, 132.7, 132.7, 135.9, 141.9, 145.9; HRMS (FAB+, direct inlet) [M]: calcd for $C_{37}H_{28}NaO_2$: 527.1987. Found: 527.1973 (Found: C, 88.01; H, 5.53. $C_{37}H_{28}O_2$ requires C, 88.07; H, 5.59).

4.2.4. (−)-(1*S*,4*R*,5*S*,8*R*)-4,8-Di(2-methoxyphenyl)-2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene-4,8-diol (–)-6. The title compound was synthesized following the general procedure, from (–)-**2** (0.100 g, 0.403 mmol) and (2-methoxyphenyl)-lithium (0.5 M in THF, 3.2 mL, 1.6 mmol). The residue was purified by column chromatography (SiO_2, pentane–ether 80:20 → 50:50) to give (–)-**6** (166 mg, 89%) in >99% ee as a white solid: mp 263–265 °C (from EtOH); $[\alpha]_D^{20} = -84$ (*c* 0.96, $CHCl_3$); IR (KBr) 3537, 3501 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.93 (2H, t, $J = 3.3$ Hz), 3.62 (2H, t, $J = 3.3$ Hz), 4.11 (6H, s), 4.69 (2H, s), 6.20–6.22 (2H, m), 6.69–6.73 (2H, m), 6.99–7.01 (2H, m), 7.21–7.30 (6H, m), 7.40–7.49 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.2, 42.2, 55.8, 80.0, 111.5, 120.5, 126.6, 127.7, 128.6, 129.7, 131.4, 131.7, 136.7, 137.0, 139.5, 156.6; HRMS (FAB+) calcd for $C_{31}H_{28}NaO_4$: 487.1885. Found: 487.1884. (Found: C, 80.04; H, 6.03. $C_{31}H_{28}O_4$ requires C, 80.15; H, 6.08).

4.2.5. (+)-(1*R*,5*R*,8*S*)-8-Hydroxy-8-(1-naphthyl)-2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene-4-one (+)-7. 1-NaphthylMgBr (1 M in THF, 2.4 mL, 2.4 mmol) was added to a mixture of (+)-**2** (0.50 g, 2.0 mmol) in ether (40 mL) at rt under an argon atmosphere. The resulting mixture was stirred at rt for 1 h after which satd NH_4Cl (50 mL) was added and the mixture was stirred for another 15 min. The phases were separated and the resulting aqueous phase was extracted with EtOAc (3×30 mL) and dried over Na_2SO_4. The solvent was removed at a reduced pressure and the residue recrystallized from ether to give (+)-**7** (0.66 g, 88%) of >99% ee as white crystals: TLC R_f 0.48, red spot (heptane–EtOAc 1:1); mp 240–242 °C; $[\alpha]_D^{20} = +208$ (*c* 1.19, $CHCl_3$); IR (KBr) 3453, 1673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.33 (1H, br s), 2.38 (1H, ddd, $J = 13.8$, 3.5, 2.4 Hz), 2.47 (1H, ddd, $J = 13.7$, 4.2, 2.4 Hz), 3.89 (1H, t, $J = 2.6$ Hz), 4.28 (1H, m), 6.58 (1H, dd, $J = 7.4$, 1.0 Hz), 7.23 (1H, triplet of multiplets, $J = 7.7$ Hz), 7.40–7.46 (2H, m), 7.31–7.35 (2H, m), 7.51–7.55 (1H, m), 7.58 (1H, ddd, $J = 8.0$, 6.8, 1.1 Hz), 7.70 (2H, m), 7.81 (1H, d, $J = 8.1$ Hz), 7.93 (1H, doublet of multiplets, $J = 3.2$ Hz), 7.95 (1H, doublet of multiplets, $J = 4.3$ Hz), 8.04 (1H, dd, $J = 7.8$, 1.4 Hz), 9.46 (1H, d, $J = 8.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.7, 43.6, 48.6, 80.0, 124.3, 125.7, 126.1, 127.4, 128.5, 128.5, 128.8, 128.9, 129.3, 129.6, 129.7, 130.0, 130.1, 130.9, 131.2, 132.2, 133.5, 135.3, 141.5, 142.1, 197.2 (two hidden peaks 124.3–142.1); HRMS (FAB+, direct inlet) [M+H]: calcd for $C_{27}H_{21}O_2$: 377.1542. Found: 377.1533 (Found: C, 85.98; H, 5.31. $C_{27}H_{20}O_2$ requires C, 86.14; H, 5.36).

4.2.6. (+)-(1*R*,5*R*,8*S*)-8-Methoxy-8-(1-naphthyl)-2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene-4-one (+)-8. A solution of (+)-**7** (150 mg, 0.4 mmol) in THF (5 mL) was added to a mixture of NaH (40 mg, 1.0 mmol) in THF (10 mL) at

0 °C under an argon atmosphere. The resulting mixture was stirred at 0 °C for 25 min and then MeI (174 μL, 2.79 mmol) was added. The mixture was stirred at 0 °C for another 5 min and then at rt overnight after which water (10 mL) was added. The layers were separated and the aqueous phase extracted with EtOAc (3 × 20 mL). The collected extracts were washed with satd $NaHCO_3$ (3 × 60 mL), dried over Na_2SO_4 and the solvent was removed at reduced pressure. The residue was purified by column chromatography (SiO_2, pentane–acetone 95:5, TLC R_f 0.29) to give (+)-**8** (153 mg, 98%) of >99% ee as a white solid: mp 225–226 °C; $[\alpha]_D^{20} = +126$ (*c* 1.03, $CHCl_3$); IR (KBr) 1683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.32 (1H, dt, $J = 13.5$, 2.8 Hz), 2.40 (1H, ddd, $J = 13.6$, 3.9, 2.7 Hz), 2.65 (3H, s), 3.88 (1H, m) 4.28 (1H, m), 6.67 (1H, dd, $J = 7.4$, 0.8 Hz), 7.23 (1H, t, $J = 7.8$ Hz), 7.29–7.40 (3H, m), 7.43 (1H, td, $J = 7.8$, 1.0 Hz), 7.52–7.62 (2H, m), 7.66 (1H, td, $J = 7.5$, 1.4 Hz), 7.76 (1H, m), 7.81 (1H, d, $J = 8.1$ Hz), 7.95 (1H, d, $J = 7.9$ Hz), 8.00 (1H, d, $J = 7.6$ Hz), 8.07 (1H, dd, $J = 7.8$, 1.2 Hz), 9.53 (1H, d, $J = 8.8$ Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 31.2, 44.1, 48.6, 56.1, 87.8, 124.3, 125.6, 126.2, 127.9, 128.0, 128.2, 128.4, 128.8, 129.4, 129.6, 129.7, 129.7, 130.9, 131.5, 131.7, 132.0, 133.8, 135.4, 135.5, 136.8, 143.2, 144.5, 197.2; HRMS (FAB+, direct inlet) [M]: calcd for $C_{28}H_{22}O_2$: 390.1620. Found: 390.1604 (Found: C, 86.09; H, 5.62. $C_{28}H_{22}O_2$ requires C, 86.13; H, 5.68).

4.2.7. (−)-(1*R*,4*S*,5*R*,8*S*)-4,8-Di(1-naphthyl)-8-methoxy-2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene-4-ol (–)-9. 1-NaphthylMgBr (1 M in THF, 1.8 mL, 1.8 mmol) was added in portions to a solution of (+)-**8** (0.292 mmol, 114 mg) in dry THF (1.5 mL) at rt, under an argon atmosphere. The resulting mixture was stirred at rt for 5 h whereafter aqueous satd NH_4Cl (3 mL) was added. The aqueous phase was extracted with ethyl acetate (3 × 10 mL) and the combined organic phases were washed with aqueous satd $NaHCO_3$ and dried over Na_2SO_4. The solvent was removed at a reduced pressure and the residue purified by column chromatography (Al_2O_3, heptane–EtOAc 80:20) to give (–)-**9** (84 mg, 54%) of >99% ee as a white solid: TLC R_f 0.6 (Al_2O_3, heptane–EtOAc 75:25); mp 245–247 °C; $[\alpha]_D^{20} = -125$ (*c* 0.27, $CHCl_3$); IR (KBr) 3450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.78–1.91 (2H, m), 2.54 (1H, s), 2.81 (3H, s), 3.96–4.02 (1H, m), 4.07–4.12 (1H, m), 6.29 (1H, d, $J = 7.3$ Hz), 6.92 (1H, dd, $J = 7.4$, 1.1 Hz), 7.06–7.15 (2H, m), 7.38 (1H, td, $J = 7.7$, 1.4 Hz), 7.4–7.44 (2H, m), 7.48 (1H, td, $J = 7.4$, 1.3 Hz), 7.50–7.61 (m, 4H), 7.65–7.75 (m, 4H), 7.88 (2H, doublet of multiplets, $J = 8.1$ Hz), 8.02 (d, 2H, $J = 7.8$ Hz), 9.51 (2H, d, $J = 8.7$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 42.6, 42.8, 56.7, 81.8, 89.7, 124.1, 124.1, 125.4, 125.4, 125.8, 126.0, 127.7, 127.7, 127.8, 127.8, 128.1, 128.3, 129.1, 129.2, 129.5, 129.5, 129.6, 129.8, 129.8, 131.3, 131.6, 131.9, 132.2, 132.5, 135.2, 135.3, 137.6, 138.2, 138.9, 142.7, 142.7, 143.1; HRMS (FAB+, direct inlet) [M]: calcd for $C_{38}H_{30}NaO_2$: 541.2143. Found: 541.2146 (Found: C, 88.01; H, 5.53. $C_{38}H_{30}O_2$ requires C, 88.00; H, 5.83).

4.2.8. (+)-(1*R*,4*S*,5*R*,8*S*)-4-Benzylamino-8-(1-naphthyl)-2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene-8-ol (+)-10. Benzylamine (0.46 mL, 4.2 mmol) was added to a mixture of (+)-**7** (200 mg, 0.5 mmol) and 4 Å molecular sieves in toluene (2 mL). The resulting mixture was stirred at reflux temperature for 22 h and then cooled to ambient temperature. The mixture was filtered, the molecular sieves were washed with EtOAc (3 × 10 mL) and the solvent removed at reduced pressure to give the benzyl imine as a pale yellow oil, which was used directly in the next step; TLC R_f 0.57, blue spot (heptane–EtOAc 1:1). $NaBH_4$ (80 mg, 2.1 mmol) was added to a mixture of the benzyl imine in MeOH (20 mL). The resulting mixture was stirred at reflux temperature for 2.5 h and then cooled to rt after which water (20 mL) was added and worked up as follows: extraction with EtOAc (3 × 15 mL) followed by drying (Na_2SO_4) and removal of the solvent at reduced pressure. The residue was purified by column chromatography (SiO_2, pentane–ether 85:15) to give (+)-**10** (127 mg, 52%) of >99% ee as a white solid: TLC R_f 0.52, blue spot (heptane–EtOAc 1:1,); mp 94–96 °C; $[\alpha]_D^{20} = +66$ (*c* 0.79, $CHCl_3$); IR (KBr) 3545, 3475 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.68 (1H, br s), 2.04 (1H, d_{AB}, $J = 13.1$ Hz), 2.36 (1H, d_{AB}, $J = 13.1$ Hz), 2.43 (1H, s), 3.60 (1H, br s), 4.07 (1H, s), 4.19 (1H, d, $J = 6.8$ Hz), 4.22 (1H, d_{AB}, $J = 13.5$ Hz), 4.48 (1H, d_{AB}, $J = 13.5$ Hz), 6.49 (1H, d, $J = 6.8$ Hz), 7.25–7.42 (7H, m), 7.46 (2H, t, $J = 7.2$ Hz), 7.55–7.69 (4H, m), 7.74 (1H, t, $J = 7.5$ Hz), 7.83 (2H, t, $J = 8.7$ Hz), 7.96 (1H, d, $J = 7.9$ Hz), 8.07 (1H, d, $J = 6.7$ Hz), 9.54 (1H, d, $J = 8.4$ Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 29.1, 33.5, 42.9, 51.3, 61.3, 82.2, 124.2, 125.4, 125.8, 126.5, 127.2, 127.7, 127.8, 127.9, 128.3, 128.6, 128.6, 128.7, 128.8, 129.1, 129.4, 129.9, 130.1, 131.3, 131.6, 135.2, 135.7, 136.1, 140.3, 140.9, 142.4, 143.2; HRMS (FAB+, direct inlet) [M]: calcd for $C_{34}H_{29}NNaO$: 490.2147. Found: 490.2127 (Found: C, 87.26; H, 6.18; N, 2.87. $C_{34}H_{29}NO$ requires C, 87.33; H, 6.25; N, 3.00).

4.2.9. (+)-(1*R*,4*S*,5*R*,8*S*)-4-Amino-8-(1-naphthyl)-2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene-8-ol (+)-11. Pd/C 5% (25 mg) and formic acid (1.25 mL) were added to a solution of (+)-**10** (96 mg, 0.2 mmol) in methanol (5 mL). The resulting slurry was stirred under a nitrogen atmosphere at rt for 5 h. The mixture was filtered through a pad of Celite, which was rinsed with a small amount of formic acid. The filtrate was neutralized by 2 M NaOH, extracted with EtOAc, dried over anhydrous Na_2SO_4 and the solvent removed at a reduced pressure. The residue was purified by column chromatography (SiO_2, heptane–EtOAc–MeOH–NH_4OH 57:38:4:1, TLC R_f 0.13) to give (+)-**11** (69 mg, 90%) in >99% ee as a white solid: mp 149–153 °C; $[\alpha]_D^{20} = +8.9$ (*c* 0.9, $CHCl_3$); IR (KBr) 3554, 3365, 3295 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.90–2.17 (2H, br s), 2.07 (1H, s), 2.07 (1H, ddd_{AB}, $J = 13.6$, 4.3, 2.1 Hz), 2.27 (1H, ddd_{AB}, $J = 13.6$, 4.3, 2.1 Hz), 3.20–3.26 (1H, m), 4.03 (1H, d, $J = 2.2$ Hz), 4.32 (1H, d, $J = 5.0$ Hz), 6.38 (1H, d, $J = 7.3$ Hz), 7.19 (1H, t, $J = 7.9$ Hz), 7.28–7.40 (4H, m), 7.40–7.46 (1H, m), 7.51–7.59 (2H, m), 7.65–7.72 (2H, m), 7.78 (1H, d, $J = 8.1$ Hz), 7.83 (1H, dd, $J = 7.5$, 1.3 Hz), 7.92 (1H, d, $J = 8.2$ Hz), 9.47 (1H, d, $J = 8.8$ Hz); ^{13}C NMR (400 MHz, $CDCl_3$) 29.3, 40.3, 43.1, 55.6, 82.2, 124.2, 125.5, 125.8, 126.7, 127.4, 127.7, 127.8, 128.1, 128.2, 129.2, 129.5, 129.9, 130.1, 130.2, 131.3, 132.1, 135.2, 135.4, 135.6, 140.7, 142.5, 143.1; HRMS (FAB+,

direct inlet) [M]: calcd for $C_{27}H_{23}NO$: 377.1780. Found: 377.1760 (Found: C, 85.86; H, 6.08; N, 3.64. $C_{27}H_{23}NO$ requires C, 85.91; H, 6.14; N, 3.71).

4.2.10. General procedure for the asymmetric hetero-Diels–Alder reactions. The procedure reported by Rawal et al. was followed using 20 mol % of catalyst **1**–**13** (0.1 mmol), diene **14** (144 μL, 0.5 mmol) and aldehyde **15** or **16** (1 mmol) in toluene (0.5 mL). The reaction mixtures were stirred at −40 °C for 48 h before the temperature was decreased to −78 °C and CH_2Cl_2 (2 mL) followed by AcCl (71 μL, 1 mmol) were added. After additional stirring for 15 min, satd $NaHCO_3$ (2 mL) and H_2O (2 mL) were added, the phases were separated and the aqueous phase extracted with CH_2Cl_2 and dried over Na_2SO_4. The residues were adsorbed on SiO_2 and purified in equipment for parallel chromatography using 10 g Isolute SiO_2 columns (heptane–EtOAc 80:20). The structures of the products were established by ^1H NMR spectroscopy and the enantiomeric excesses determined by enantioselective HPLC.

4.2.11. Molecular mechanics details. In the molecular mechanics calculations, we used the empirical force field MM3*, with default parameters, as implemented in MACROMODEL v.6.5. MM3* differs from the authentic field by use of Coulomb's law treatment of electrostatics and in the torsional barrier treatment of conjugation. The Polak–Ribiere conjugate gradient algorithm was applied in all minimizations with a 500 iteration limit, and a cut-off of 12 Å was used for the nonbonded interactions. Energy convergence criterion was 0.05 kJ/mol. In the Monte Carlo conformational search default settings were utilized, except that 500 Monte Carlo steps were carried out. The energy range for stored structures was 50 kJ/mol. Full matrix Newton–Raphson minimization method (FNMR) was applied to the low energy structures found in the conformational search. Minimization of the low energy structures were refined by the AMBER*, OPLS* and MMFF(s) force fields giving very similar results. All calculations were performed in the gas phase.

Five competitive conformations were found in the Monte Carlo search, which were reduced to three conformations after FNMR refinement. In all these structures the benzaldehyde aromatic ring was stacked, but parallelly displaced, with respect to one of the two aromatic rings in the catalyst.

Conformation	Energy (kJ/mol)
*R*1	234.34
*R*2	236.11
S	236.08

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