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Stereoselective oxazaborolidine–borane reduction of biphenyl alkyl ketones

Giovanna Delogu,[a,*] Davide Fabbri,[a] Cristina de Candia,[a] Angela Patti[b,*] and Sonia Pedotti[b]

[a]*Istituto di Chimica Biomolecolare del CNR, Sez. di Sassari, Traversa la Crucca 3, regione Baldinca, Li Punti, 07040 Sassari, Italy*

[b]*Istituto di Chimica Biomolecolare del CNR, Sez. di Catania, Via del Santuario 110, I-95028 Valverde CT, Italy*

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Abstract—Asymmetric reduction of three different biphenyl alkyl ketones with (*R*)-oxazaborolidine **1** as catalyst was successfully carried out and the corresponding biphenyl alcohols were obtained in high yield and e.e. High diastereoselectivity was achieved with the C_2-symmetric, configurationally stable biphenyl **6** and more detailed investigations evidenced a cooperative effect between stereoaxis and stereocentre.

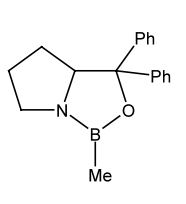
1. Introduction

Enantiopure alkylaryl carbinols have received considerable interest as building blocks for the preparation of chiral drugs and ligands by virtue of the hydroxyl group which can be further functionalised to afford amino, sulphur and phosphorus derivatives.[1] Asymmetric reduction of a carbonyl group is a direct route to chiral alcohols and in this context efficient reductive methods have been developed.[2–4] However, the effectiveness of the reduction process is dictated by the nature of the ketone and the choice of chiral ligand, thus, a reagent system with general applicability is not yet available.

As part of an ongoing program on the preparation of hydroxylated biphenyls,[5] we focused our attention on the asymmetric reduction of functionalised prochiral biphenyl ketones catalysed by CBS–oxazaborolidine. The CBS method, developed by the groups of Itsuno[2a] and Corey,[2c] offers simplicity of procedure, high yields, high enantioselectivities and a wide range of applicability particularly with alkylaryl ketones.[6] Although rational modifications of the CBS catalyst structure allowed optimal enantioselectivity to be achieved for specific substrates,[7] the boron methyl derivative of oxazaborolidine of α,α-diphenyl prolinol (CBS-Me) **1**, is often the catalyst of choice due to its stability and commercial availability in both enantiomeric forms.

To our knowledge, very little attention has been paid to the asymmetric reduction of biphenyl alkyl ketones via chemical[8] as well as enzymatic[9] methods and, in all examples, only configurationally flexible biphenyls have been reported. If the biphenyl ketone is configurationally stable, the stereogenic axis could be involved in the formation of the alcohol and different configurations at the biphenyl moiety can be envisaged for each prostereogenic centre.

Enantiopure C_2-symmetric biphenyl carbinols are valuable intermediates in the preparation of new ligands[8b,10] and are also useful models for understanding the biosynthesis and stereochemistry of naturally occurring compounds which possess the biphenyl structure.[11] In the synthesis of lignin, the presence of dimeric neolignans e.g. **2** plays an important role in understanding the factors which govern the coupling and cross-coupling of the phenol units.[12]



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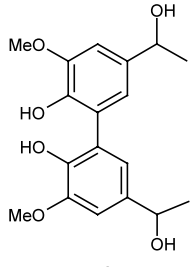

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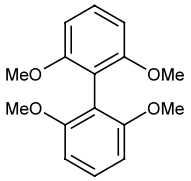

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* Corresponding authors. E-mail: g.delogu@iatcapa.ss.cnr.it; patti@issn.ct.cnr.it

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The aim of the work we report herein was to apply the effectiveness of the oxazoborolidine-catalysed reduction of prochiral biphenyl ketones to investigate the influence of a C_2-symmetry axis and to observe the possible chiral cooperative effect between stereocentres and stereoaxis in conformationally stable biphenyls.[13]

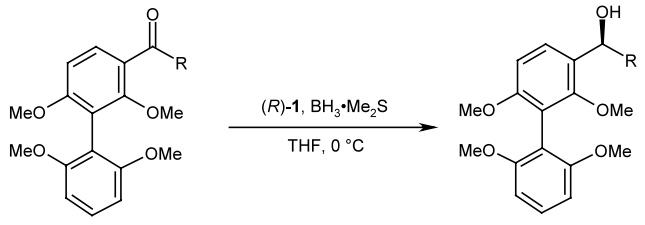
We focused our attention on tetramethyl tetrol **3** as a building block to prepare ketones **4–6** since, according to the substitution at the biphenyl skeleton with the acyl group, we could investigate different CBS-discriminating effects. In fact, the carbonyl faces are enantiotopic in achiral ketones **4–5**, and diastereotopic in diketone (±)-**6**, which is a racemic mixture of atropisomers. Ketones **4–6**, which were prepared in good yield by known and direct methods,[14] resemble the structure of naturally occurring biphenyls.

2. Results and discussion

2.1. Preparation of chiral alkyl biphenyl carbinols

At the outset of our work we decided to investigate the CBS-Me catalysed reduction of prochiral monoketones **4** and **5**. Due to the presence of the same groups on 2′- and 6′-positions of the biphenyl backbone, compounds **4** and **5** are not racemic mixtures, despite their blocked conformation. Thus, they seemed good substrates to test the reactivity and enantioselectivity in the CBS-Me-catalysed hydrogenation of a carbonyl group embedded in a rigid biphenyl system without considering the influence of axial chirality on the course of the reaction.

When ketone **4** was reduced in THF at 0°C in the presence of 30 mol% of (*R*)-**1** with $BH_3{\cdot}Me_2S$ as the hydride source (Scheme 1), quantitative conversion of the substrate into the corresponding alcohol (−)-**7** was reached after addition of the reagents. After isolation of (−)-**7**, its enantiomeric purity was determined as >95% by ^{1}H NMR analysis of the corresponding acetate in the presence of Eu(hfc)$_3$. To evaluate the effects of the steric hindrance of the substituent on the carbonyl group, the same reaction was performed using ketone **5** as substrate and alcohol (−)-**8** was obtained in 83% isolated yield and 93% e.e. (by chiral HPLC) after 5 h. Assignment of (*S*)-configuration at the stereogenic centre of (−)-**7** and (−)-**8** was deduced from the known stereochemical course of oxazaborolidine-catalysed reductions of ketones.[2c]



4 R = Me
5 R = *t*-Bu

(−)-**7** R = Me
(−)-**8** R = *t*-Bu

Scheme 1.

Reduction of the catalyst loading to 10 mol% using ketone **4** as the substrate led to a marked decrease in both the reaction rate and enantioselectivity. After 5 h the reaction mixture contained 88% of alcohol (−)-**7** in 58% e.e. In the case of compound **5**, after 24 h only 20% conversion of the starting material was obtained and the e.e. of (−)-**8** dropped to 40%. It therefore seems evident that a higher reaction rate is essential to obtain good enantioselectivity; despite the different steric hindrance exerted by the methyl and *tert*-butyl groups, good levels of asymmetric induction were obtained providing that a suitable amount of the catalyst was used.

We then considered (±)-**6** as a substrate, taking into account that CBS-Me-catalysed reaction has been reported as a tool for the kinetic resolution of racemic compounds possessing axial or planar chirality through enantioselective reduction by the oxazaborolidine–borane system.[15] On the other hand, enantioenriched compounds can, in principle, be obtained by stereoselective conversion of both enantiomers of a racemic mixture into different diastereomers through the creation of a new stereogenic centre.

Preliminary chemical reduction of (±)-**6** with $NaBH_4$ afforded three diastereomeric diols **9a–c** in a ratio of 3:4:1, respectively, as determined by ^{1}H NMR analysis of the reaction mixture in the presence of Eu(fod)$_3$ and integration of -OMe singlet resonances. Optimisation of the purification conditions by column chromatography afforded pure diols (±)-**9a**, (±)-**9b** and (±)-**9c**. The NMR spectra revealed the presence of a C_2-symmetry axis in diols (±)-**9a** and (±)-**9c** as expected for atropodiastereomers possessing (*RR*)- or (*SS*)-configuration at the stereogenic carbons. In the case of diol (±)-**9b** all the proton resonances were doubled, apart from a singlet at δ 3.77, indicating that the molecule is not symmetrical as a consequence of the (*RS*)-configuration at the stereogenic carbons.

The asymmetric reduction of (±)-**6** with 60 mol% (*R*)-**1** proceeded with high reaction rate (complete conversion after 30 min at 0°C) giving a mixture of the three diastereomeric diols **9a–c** in a 49:12:39 ratio. C_2-Symmetric diols (−)-**9a** and (−)-**9c** were obtained in nearly enantiopure form, with 95 and >98% e.e., respectively, whereas diol (−)-**9b** was recovered with 80% e.e. (Table 1, entry 1), as measured by chiral HPLC (Scheme 2).

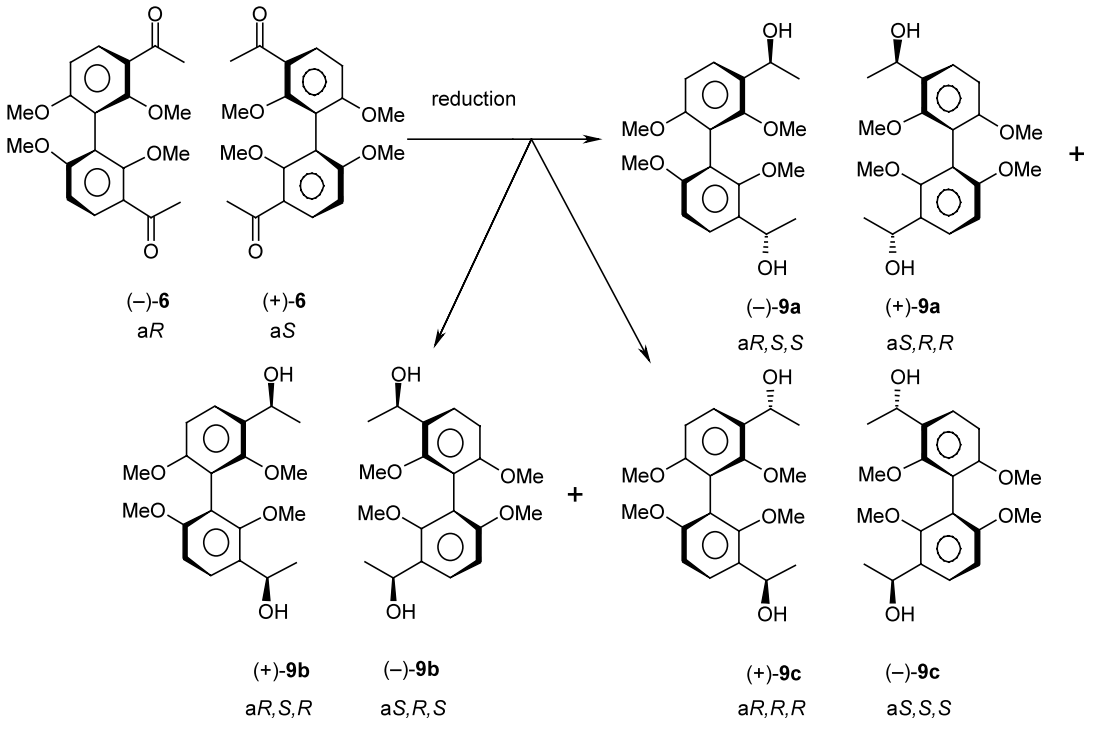
The oxidation of (−)-**9a** with MnO_2 gave ketone (−)-**6** (95% e.e.) whose absolute configuration was assigned as a*R* based on the comparison of its CD Cotton effects with those of other known biphenyl diketones.[16] The same reaction was carried out on alcohol (−)-**9c** to prepare enantiopure (+)-**6** with (a*S*)-absolute configuration.

The absolute configuration of (−)-**9b** was unequivocally deduced as a*S*,*R*,*S* on the basis of its dissymmetric nature and the formation of (+)-**6** by oxidation. The *S* assignment of the configuration at both stereogenic centres of (−)-**9a** and (−)-**9c** was deduced from the

Table 1. (*R*)-**1** catalysed reduction of biphenyl methyl ketones

Entry	Substrate	Catalyst (mol%)	Time (h)	(−)-**9a**, %[a] (% e.e.)[b]	(−)-**9b**, %[a] (% e.e.)[c]	(−)-**9c**, %[a] (% e.e.)[c]
1	(±)-**6**	60	0.5	49 (95)	12 (80)	39 (>98)
2	(±)-**6**	20	24	46 (92)	23 (52)	31 (>98)
3	(±)-**10a**	10	5	55 (80)	45 (>98)	–
4	(±)-**10b**	10	8	–	58 (61)[d]	42 (84)

[a] % Ratios determined by ^{1}H NMR of the reaction mixture in the presence of Eu(fod)$_3$.
[b] Determined by chiral HPLC after oxidation to the corresponding diketone.
[c] Determined by chiral HPLC.
[d] The isolated alcohol in this case is (+)-**9b**.



Scheme 2. Stereoisomeric diols deriving from reduction of racemic diketone **6**.

known stereochemical course of oxazaborolidine-catalysed reductions of ketones, as previously mentioned for alcohols (−)-**7** and (−)-**8**.

2.2. Diastereoselectivity and cooperative effect in the CBS–borane reduction of (±)-6

Although the mechanism of the CBS-catalysed reduction with boranes is well-known, only few examples are reported for the application of this reaction to prochiral diketones to afford diastereoisomeric alcohols due to the presence of two carbonyl groups.[8a,17] Additional stereoisomers can derive from the presence of two enantiomeric forms in the substrate, as in diketone (±)-**6**, so that the final composition of the reaction mixture and enantiomeric excess of the products depend on different factors and are not easily predictable.

As previously highlighted,[18] in the asymmetric transformation of a racemic substrate with the creation of one or more stereogenic centres, the formation of products with high e.e. is not automatically associated with a good kinetic resolution process and some conclusions can be reached from the study of a partial conversion of the racemic mixture. Thus, we performed the reduction of (±)-**6** using 20 mol% of the catalyst in order to decrease the reaction rate. The analysis of an aliquot of the reaction mixture after 1 h (24% conv.), when no diols were detected, showed that the unreacted ketone **6** had (a*S*)-absolute configuration with only 4.6% e.e. The calculated[19] stereoselectivity factor $s = k_{rel} = 1.4$ indicated that both enantiomers of (±)-**6** reacted with about the same reaction rate excluding a kinetic resolution process.

The formation of two intermediate monoketones **10a** and **10b** was observed by TLC analysis, but all attempts to isolate them in order to measure their e.e. failed due to their low concentration in the reaction mixture. In order to increase the formation of **10a** and **10b**, the reaction was allowed to stand for a longer time, but no significant increase in the amount of these transient monoketones was observed. After 24 h, complete con-

version of (±)-**6** was achieved and diols (−)-**9a** and (−)-**9c** were recovered with high e.e. values of 92 and >98%, respectively (Table 1, entry 2), unlike that observed in the case of monoketones **4** and **5** when 10 mol% of (*R*)-**1** was used.

This is an interesting result in view of scale-up of the asymmetric reduction of (±)-**6**; the occurrence of a less stereoselective reduction of the carbonyl group, e.g. larger amount of (*R*)-configuration at the new stereocentres, is reflected in a larger amount of (−)-**9b** with low enantiomeric purity (52% e.e.), but symmetrical diols (−)-**9a** and (−)-**9c** are still recovered in good yield and e.e. If there was a decrease in the stereoselectivity to the same extent for all steps of the reduction using less catalyst, a lower enantiomeric excess of products should be expected. This is not the case for (−)-**9a** and (−)-**9c** when the catalyst is used at a loading of 20 mol%, whereas a marked decrease in enantiomeric excess was evident for (−)-**9b**, so the observed reaction course can be explained by considering different diastereoselectivities for each enantiomer of (±)-**6** and the intermediate monoketones.

The determination of selected diastereomeric ratios might support this hypothesis and evidence matched/mismatched effects between axial and central chirality. Unfortunately, it is not possible to determine the facial diastereoselectivity at each stereocentre of (±)-**6**, since diol **9b** can be formed from all of the four stereoisomers of **10a** and **10b**. Therefore, we prepared racemic monoketones (±)-**10a** and (±)-**10b** as new substrates for CBS-catalysed reductions.

The availability of (±)-**10a** and (±)-**10b** should simplify the evaluation of the facial diastereoselectivity due to the presence of only one carbonyl group in the substrate, although the likelihood of different coordination of chiral CBS with monoketones with respect to (±)-**6** should be taken into account.

The configuration at the stereogenic centre as well as the stereoaxis was deduced as a*R*,*S*/a*S*,*R* for (±)-**10a** and a*R*,*R*/a*S*,*S* for the diastereoisomeric (±)-**10b** from the analysis of the products obtained in the reduction with $NaBH_4$. Actually, monoketone (±)-**10a** gave diols (±)-**9a** and (±)-**9b**, whereas (±)-**10b** afforded diols (±)-**9b** and (±)-**9c** (Scheme 3).

We then performed the reduction of monoketone (±)-**10a** using 10 mol% of (*R*)-**1**; after 5 h complete conversion of the substrate was achieved and diol (−)-**9a** (e.e. 80%) and enantiopure (−)-**9b** (>98% e.e.) in a 1.2:1 ratio were formed (Table 1, entry 3).

Applying Kagan's equations,[18] facial diastereoselectivities were calculated as:

$$a_1=\frac{[\mathrm{a}R,S,S']}{[\mathrm{a}R,S,R']}=110 \text{ and } \mathrm{b}_1=\frac{[\mathrm{a}S,R,S']}{[\mathrm{a}S,R,R']}=8.1$$

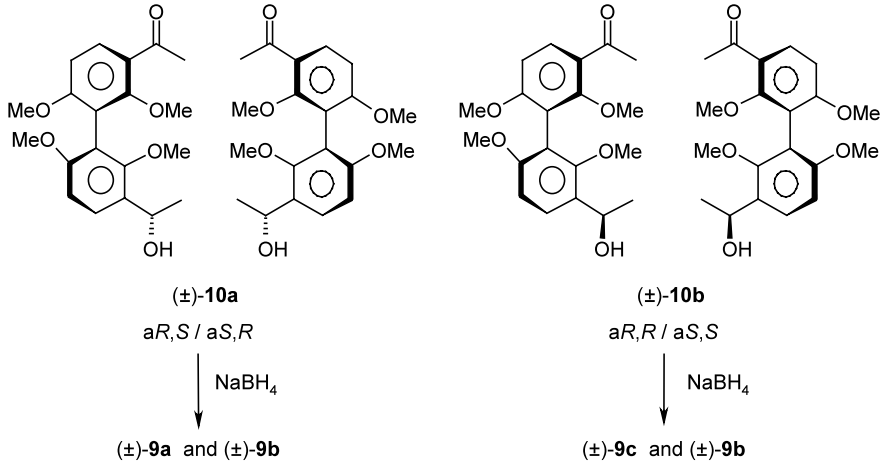
where S' and R' refer to the new formed stereocentres.[20]

Different facial diastereoselectivities were calculated when the reaction was carried out on (±)-**10b** (Table 1, entry 4) as:

$$a_2=\frac{[\mathrm{a}R,R,S']}{[\mathrm{a}R,R,R']}=13.9 \text{ and } b_2=\frac{[\mathrm{a}S,S,S']}{[\mathrm{a}S,S,R']}=3.4.$$

These diastereoselectivity values indicate that the (*S*)-configuration at the two stereogenic centres is always preferred and the presence of a stereoaxis should be considered. In fact, the axial chirality enables to drive the attack of the reducing agent on the opposite faces of the carbonyl groups to a different extent. The effects of chiral cooperativity between stereocentre and stereoaxis are evident and the (a*R*,*S*)-configuration seems to be the best matched couple as determined from the first equation above ($a_1=110$). The lower global selectivity observed for atropisomer a*S* is responsible for the formation of both (−)-**9b** and (−)-**9c**, whereas the atropisomer a*R* is almost exclusively converted into the diol (−)-**9a**.

The observed diastereofacial selectivities refer to the reaction with 20 mol% of (*R*)-**1** and should presumably be higher when the catalyst loading is increased, as the



Scheme 3.

better e.e.s found for the recovered diols and the reduced amount of (−)-**9b** isolated in the reaction carried out using 60 mol% of (*R*)-**1** indicate (cf. entries 1 and 2 in Table 1).

3. Conclusions

This is the first example of reduction of non-planar biphenyl alkyl ketones with CBS system. We highlighted the effect of chiral cooperativity between a stereoaxis and a stereocentre in the diastereoselectivity of the reduction process. High diastereoselectivities were obtained leading to C_2-symmetric biphenyl diols in good yield. Further investigations of this methodology in the preparation of enantiopure biphenyl carbinols are currently in progress.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AMX 250 or Bruker Avance™ 400 spectrometers. Chemical shift (δ) are given as ppm relative to the residual solvent peak. Coupling constants (J) are in Hz. Melting points are uncorrected. Optical rotations were measured on a DIP 135 JASCO instrument. THF was distilled under argon from sodium benzophenone ketyl. (*R*)-Methyl-CBS–oxazaborolidine, (*R*)-**1** was purchased from Aldrich as 1 M solution in toluene. All the CBS-Me-catalysed reactions were carried out under argon using standard Schlenk techniques. Column chromatography was performed on silica gel 60 (70–230 mesh) or LiChroprep® Si 60 (25–40 μm) using the specified eluants. Chiral HPLC analyses were carried out on Chiracel® OD column (Daicel Chemical Industries) using *n*-hexane/*iso*-propanol mixtures as a mobile phase and detection by UV–vis detector at 225 nm. CD spectra of (−)-**6** and (+)-**6** were registered at room temperature in ethanol (0.1 cm cell length, 4.52×10^{-4}M) on a JASCO J-810 spectropolarimeter.

4.2. General procedure for the asymmetric reduction

In a typical procedure, (*R*)-**1** (30 mol%, 0.19 mmol, 0.19 mL of 1 M solution in toluene) was dissolved in THF (8 mL) under argon and cooled to 0°C. From a syringe charged with $BH_3{\cdot}Me_2S$ (2 M in THF, 0.315 mL, 0.63 mmol), 20% of the final amount were added to the catalyst solution. After 10 min of stirring, the remaining $BH_3{\cdot}Me_2S$ and a solution of ketone **4** (200 mg, 0.63 mmol) were simultaneously added by syringe pump within 20 min. The reaction mixture was then stirred at room temperature and stopped when quantitative conversion of the substrate was observed by TLC analysis. At completion, the reaction was quenched by careful dropwise addition of MeOH (2 mL), diluted with satd NH_4Cl and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and taken to dryness under vacuum to give a residue that was purified by column chromatography.

4.3. 1-(2,2′,6,6′-Tetramethoxy-1,1′-biphenyl-3-yl)-ethanone 4

To a stirred mixture of **3** (1 g, 3.65 mmol) and acetyl chloride (0.31 g, 4 mmol) under N_2, iodine (0.036 g, 0.14 mmol) was added. The mixture was stirred at 120°C for 24 h. The crude reaction mixture was poured into ice water and extracted with CH_2Cl_2. The organic extract was washed successively with dilute sodium carbonate, sodium bisulfite and water and dried over Na_2SO_4.

The solution was concentrated to afford a brown solid that was purified by flash chromatography (CH_2Cl_2/petroleum, 1:5) to give **4** (0.87 g, 75%): mp 82–3°C; ^{1}H NMR δ 2.63 (3H, s, MeCO-), 3.44 (3H, s, -OMe), 3.73 (6H, s, OMe), 3.75 (3H, s, OMe), 6.65 (2H, d, $J=8.4$, Ar-H), 6.78 (1H, d, $J=8.8$, Ar-H), 7.34 (1H, t, $J=8.4$, Ar-H), 7.82 (1H, d, $J=8.8$, Ar-H); ^{13}C NMR δ 31.05, 56.35, 56.41, 61.59, 104.41, 106.72, 11.87, 117.98, 125.66, 129.60, 131.30, 158.33, 160.06, 162.14, 198.90. Anal. calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37; found: C, 68.53; H, 6.19%.

4.4. 2,2′-Dimethyl-1-(2,2′,6,6′-tetramethoxy-1,1′-biphenyl-3-yl)propan-1-one 5

To a solution of **3** (1.5 g, 5.46 mmol) in toluene (30 mL) under N_2, zinc (0.36 g, 5.5 mmol) and pivaloyl chloride (0.66 g, 5.5 mmol) were added. The mixture was stirred at 90°C for 12 h and then filtered. The solution was evaporated to give a colourless solid that was purified by flash chromatography (CH_2Cl_2/petroleum, 1:1) to afford **5** (1.27 g, 65%): mp 93–4°C; ^{1}H NMR δ 1.25 (9H, s, Me-C), 3.31 (3H, s, -OMe), 3.74 (6H, s, -OMe), 3.76 (3H, s, -OMe), 6.64 (2H, d, $J=8.1$, Ar-H), 6.72 (1H, d, $J=8.4$, Ar-H), 7.04 (1H, d, $J=8.4$, Ar-H), 7.32 (1H, t, $J=8.1$, Ar-H); ^{13}C NMR δ 27.39, 56.32, 56.44, 61.80, 104.46, 106.40, 111.99, 117.90, 125.90, 128.65, 129.43, 155.83, 158.34, 159.06, 214.47. Anal. calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31; found: C, 70.26; H, 7.12%.

4.5. (1*S*)-1-(2,2′,6,6′-Tetramethoxy-1,1′-biphenyl-3-yl)-ethanol (−)-7

Reduction of ketone **4** according to the procedure described above afforded a residue which was purified on Silica gel column (CH_2Cl_2/Et_2O, 9:1) to afford pure (−)-**7** as a white solid (171 mg, 85% yield, >95% e.e.), mp 100–102°C, $[\alpha]_D=-13.7$ (c 0.96, $CHCl_3$); ^{1}H NMR: δ 1.57 (3H, d, $J=6.4$, *Me*-CH), 3.44 (3H, s, -OMe), 3.74 (3H, s, -OMe), 3.76 (3H, s,-OMe), 3.77 (3H, s, -OMe), 5.18 (1H, q, $J=6.4$, -C*H*OH), 6.69 (2H, d, $J=8.4$, Ar-H), 6.80 (1H, d, $J=8.7$, Ar-H), 7.32–7.42 (2H, m,-Ar-H); ^{13}C NMR: δ 23.38, 56.10, 60.75, 65.48, 104.32, 106.78, 112.44, 117.25, 125.82, 129.17, 130.29, 156.83, 157.93, 158.32. Anal. calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97; found: C, 67.84; H, 6.89%.

4.6. (1*S*)-2,2′-Dimethyl-1-(2,2′,6,6′-tetramethoxy-1,1′-biphenyl-3-yl)propan-1-ol (−)-8

Reduction of ketone **5** according to the general procedure afforded a residue that was purified on a silica gel column (CH_2Cl_2/Et_2O, 9:1) to afford pure (−)-**8** as a white solid (164 mg, 83% yield, >95% e.e.), mp 50–52°C, $[\alpha]_D=-18.4$ (*c* 1.68, $CHCl_3$); HPLC, *n*-hexane/*i*-PrOH 85:15, flow rate 0.5 mL/min, t_R/min = 10.98 (*S*), 13.93 (*R*); ^{1}H NMR: δ 0.98 (9H, s, MeC-), 3.16 (3H, s, -OMe), 3.71(3H, s, -OMe), 3.74 (3H, s, -OMe), 3.77 (3H, s, -OMe), 4.77 (1H, s, -C*H*OH), 6.68 (2H, d, *J* = 8.3, Ar-H), 6.78 (1H, d, *J* = 8.6, Ar-H), 7.31–7.40 (2H, m, Ar-H); ^{13}C NMR: δ 25.85, 36.65, 55.91, 55.99, 56.14, 60.37, 62.43, 65.82, 104.10, 104.72, 106.05, 113.01, 116.41, 125.48, 126.52, 127.52, 127.89, 128.46, 129.03, 157.51, 157.57, 158.34. Anal. calcd for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83; found: C, 69.76; H, 7.65%.

4.7. Asymmetric reduction of (±)-6

According to the procedure described above, (±)-**6** (200 mg, 0.56 mmol) were reduced using catalyst (*R*)-**1** (0.335 mmol, 0.335 mL of 1 M solution in toluene, 60 mol%) and after the addition of $BH_3{\cdot}Me_2S$ (0.559 mL, 1.12 mmol) quantitative conversion of the substrate was observed by TLC analysis. After the work-up, the residue was purified on LiChroprep® Si 60 column eluting with CH_2Cl_2/Et_2O 3:2, then 1:1.

The first fraction contained (a*R*,1*S*,1′*S*)-1,1′-(2,2′,6,6′-tetramethoxy-1,1′-biphenyl-3,3′-diyl) diethanol (−)-**9a**: (85 mg, 42% yield, 95% e.e.); R_f 0.28 (CH_2Cl_2/Et_2O, 3:2); mp 58°C; $[\alpha]_D=-14.8$ (*c* 0.75, $CHCl_3$); ^{1}H NMR δ 1.55 (6H, d, *J* = 6.5, *Me*CH-), 2.40 (2H, bs, -OH), 3.36 (6H, s, -OMe), 3.76 (6H, s, -OMe), 5.16 (2H, q, *J* = 6.5, -C*H*OH), 6.79 (4H, d, *J* = 8.5, Ar-H), 7.44 (4H, d, *J* = 8.5, Ar-H); ^{13}C NMR δ 24.23, 55.92, 60.80, 65.89, 106.54, 117.23, 126.38, 130.74, 156.38, 157.92. Anal. calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23; found: C, 65.92; H, 7.11%. The enantiomeric excess of (−)-**9a** was measured by chiral HPLC after oxidation to the corresponding diketone **6**.

The other symmetric alcohol, (a*S*,1*S*,1′*S*)-1,1′-(2,2′,6,6′-tetramethoxy-1,1′-biphenyl-3,3′-diyl) diethanol, (−)-**9c**, was isolated in 31% yield (63 mg, >98% e.e.); R_f 0.16 (CH_2Cl_2/Et_2O, 3:2); mp 65°C; $[\alpha]_D=-23.4$ (*c* 0.43, $CHCl_3$); HPLC, *n*-hexane/*i*-PrOH 85:15, flow rate 0.7 mL/min, t_R/min = 16.66 (a*R*), 31.69 (a*S*); ^{1}H NMR δ 1.58 (6H, d, *J* = 6.5, *Me*CH-), 2.56 (2H, bs, -OH), 3.40 (6H, s, OMe), 3.78 (6H, s, -OMe), 5.23 (2H, q, *J* = 6.5, -C*H*OH), 6.81 (4H, d, *J* = 8.5, Ar-H), 7.46 (4H, d, *J* = 8.5, Ar-H); ^{13}C NMR δ 22.84, 55.92, 60.78, 64.68, 106.52, 117.04, 126.29, 130.74, 156.50, 157.98. Anal. calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23; found: C, 66.09; H, 7.14%.

The third fraction contained (a*S*,1*R*,1′*S*)-1,1′-(2,2′,6,6′-tetramethoxy-1,1′-biphenyl-3,3′-diyl) diethanol, (−)-**9b** (20 mg, 10% yield, 80% e.e.); R_f 0.21 (CH_2Cl_2/Et_2O 3:2); $[\alpha]_D=-5.2$ (*c* 0.25, $CHCl_3$); HPLC, *n*-hexane/*i*-PrOH 85:15, flow rate 0.5 mL/min, t_R/min = 18.35 (a*S*), 23.21 (a*R*); ^{1}H NMR δ 1.56 (3H, d, *J* = 6.5, *Me*CH-), 1.57 (3H, d, *J* = 6.5, *Me*CH-), 2.37 (1H, bs, -OH), 2.54 (1H, bs, -OH), 3.41 (3H, s, -OMe), 3.44 (3H, s, -OMe), 3.77 (6H, s, -OMe), 5.17 (1H, q, *J* = 6.5, -C*H*OH), 5.23 (1H, q, *J* = 6.5, -C*H*OH), 6.80 (2H, d, *J* = 8.5, Ar-H), 7.45 (1H, d, *J* = 8.5, Ar-H), 7.46 (1H, d, *J* = 8.5, Ar-H); ^{13}C NMR δ 22.87, 24.32, 55.92, 60.69, 60.89, 64.74, 65.92, 106.49, 106.55, 117.08, 117.18, 126.24, 126.40, 130.70, 130.78, 156.37, 156.52, 157.93, 157.97. Anal. calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23; found: C, 65.92; H, 7.08%.

4.8. (a*R*)-1,1′-(2,2′,6,6′-Tetramethoxy-1,1′-biphenyl-3,3′-diyl)diethanone (−)-6 and (a*S*)-1,1′-(2,2′,6,6′-tetramethoxy-1,1′-biphenyl-3,3′-diyl)diethanone (+)-6

To a solution of (−)-**9a** (50 mg, 0.14 mmol, 95% e.e.) in CH_2Cl_2 140 mg of MnO_2 were added and the suspension maintained under stirring at room temperature overnight. After removal of the black powder by centrifugation, the solution was taken to dryness to give (a*R*)-(−)-**6** (46 mg, 92% yield, 95% e.e.); $[\alpha]_D=-34.8$ (*c* 0.67, C_6H_6); HPLC, *n*-hexane/*i*-PrOH 85:15, flow rate 0.5 mL/min, t_R/min = 24.6 (a*S*), 27.2 (a*R*); CD (EtOH) λ_{ext} 313.2 ($\Delta\varepsilon$ −1.75), 284.8 ($\Delta\varepsilon$ +4.43), 261.2 ($\Delta\varepsilon$ −10.91), 218.6 ($\Delta\varepsilon$ +37.35), 201.8 ($\Delta\varepsilon$ −40.44).

In the same way, compound (−)-**9c** afforded diketone (a*S*)-(+)-**6** (>98% e.e.); $[\alpha]_D=+35.6$ (*c* 0.72, C_6H_6); CD (EtOH) λ_{ext} 313.6 ($\Delta\varepsilon$ +1.64), 284.4 ($\Delta\varepsilon$ +4.62), 260.0 ($\Delta\varepsilon$ +10.88), 219.4 ($\Delta\varepsilon$ −38.33), 201.0 ($\Delta\varepsilon$ +41.35).

4.9. Synthesis of (a*R*,*S*/a*S*,*R*)-1-[3′-(1-hydroxyethyl)-2,2′,6,6′-tetramethoxy-1,1′-biphenyl-3-yl]ethanone (±)-10a and (a*R*,*R*/a*S*,*S*)-1-[3′-(1-hydroxyethyl)-2,2′,6,6′-tetramethoxy-1,1′-biphenyl-3-yl]ethanone (±)-10b

Compound (±)-**6** (500 mg, 1.4 mmol) was dissolved in THF and a solution of $NaBH_4$ (26 mg, 0.7 mmol) in MeOH (1 mL) was added dropwise. The reaction mixture was stirred at rt and after 2 h diols **9a**–**c** began to be detected by TLC analysis. The excess $NaBH_4$ was quenched with MeOH and the reaction mixture extracted twice with AcOEt. The combined extracts were dried over Na_2SO_4 and evaporated under reduced pressure to give a residue that was purified on LiChroprep® Si 60 column eluting with CH_2Cl_2/t-BME 85:15. Unreacted (±)-**6** and diols **9a**–**c** were discarded. The first collected fraction contained compound (±)-**10a**: (151 mg, 30% yield), R_f 0.28 (CH_2Cl_2/t-BME 85:15); ^{1}H NMR δ 1.56 (3H, d, *J* = 6.5, *Me*CH-), 2.30 (1H, d, *J* = 3.7, -OH), 2.65 (3H, s, MeCO-), 3.46 (3H, s, -OMe), 3.47 (3H, s, -OMe), 3.76 (3H, s, -OMe), 3.81 (3H, s, -OMe), 5.17 (1H, m, -C*H*OH), 6.81 (1H, d, *J* = 8.6, Ar-H), 6.83 (1H, d, *J* = 8.6, Ar-H), 7.47 (1H, d, *J* = 8.6, Ar-H), 7.86 (1H, d, *J* = 8.6, Ar-H); ^{13}C NMR δ 24.24, 30.58, 55.89, 56.02, 60.96, 61.21, 65.66, 106.35, 107.18, 116.68, 117.70, 125.82, 126.59, 130.87, 131.58, 156.32, 157.83, 159.56, 161.99, 198.83. Anal. calcd for $C_{20}H_{24}O_6$: C, 66.64; H, 6.71; found: C, 66.52; H, 6.58%.

A second fraction contained compound (±)-**10b**: (81 mg, 16% yield), R_f 0.22 (CH_2Cl_2/*t*-BME 85:15); ^{1}H NMR δ 1.58 (3H, d, $J=6.5$, *Me*CH-), 2.47 (1H, bs, -OH), 2.65 (3H, s, MeCO-), 3.43 (3H, s, -OMe), 3.46 (3H, s, -OMe), 3.77 (3H, s, -OMe), 3.82 (3H, s, -OMe), 5.23 (1H, q, $J=6.5$, -C*H*OH), 6.81 (1H, d, $J=8.6$, Ar-H), 6.83 (1H, d, $J=8.6$, Ar-H), 7.48(1H, d, $J=8.6$, Ar-H), 7.87 (1H, d, $J=8.6$, Ar-H); ^{13}C NMR δ 23.05, 30.64, 55.89, 56.03, 60.88, 61.27, 64.74, 106.39, 106.59, 116.56, 117.67, 125.83, 126.57, 130.84, 131.61, 156.50, 157.88, 159.57, 162.02, 198.79. Anal. calcd for $C_{20}H_{24}O_6$: C, 66.64; H, 6.71; found: C, 66.48; H, 6.60%.

4.10. Asymmetric reduction of (±)-10a and (±)-10b

According to the procedure described above, (±)-**10a** (60 mg, 0.17 mmol) was reduced using (*R*)-**1** (0.017 mmol, 10 mol%) with $BH_3{\cdot}Me_2S$ (0.17 mmol) as the hydride source. The reaction was monitored by TLC analysis and stopped when quantitative conversion of the substrate was observed. After the work-up, the residue was purified as described above to afford (−)-**9a** (80% e.e.) and (−)-**9b** (>98% e.e.).

In the same way starting from (±)-**10b** diols (+)-**9b** (61% e.e.) and (−)-**9c** (81% e.e.) were recovered.

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