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Tropos deoxycholic acid-derived biphenylphosphites: synthesis, stereochemical characterization and use as chiral ligands in the copper catalyzed conjugate addition of diethylzinc to acyclic enones

Sarah Facchetti, Debora Losi and Anna Iuliano*

Dipartimento di Chimica e Chimica Industriale, Università di Pisa, via Risorgimento 35, 56126 Pisa, Italy

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Abstract—Three new deoxycholic acid-based 5,5′ substituted biphenylphosphites, **2**–**4**, were synthesized and their stereochemical features were examined by CD and NMR spectroscopy, which allowed us to determine the sense of twist of the substituted biphenyl moiety as well as the extent of its prevalence in different solvents. Phosphites **1**–**4** were used as chiral ligands in the copper catalyzed conjugate addition of diethylzinc to acyclic enones, affording the alkylation products with ees up to 65%. The results obtained allowed a correlation between asymmetric induction and the sense of twist of the biphenylphosphite moiety of the chiral inducers.

1. Introduction

The asymmetric copper catalyzed conjugate addition of dialkylzinc reagents to unsaturated compounds represents a straightforward methodology to form C–C bonds in an enantioselective way.[1] The success of this approach lies in the good choice for chiral ligands of the copper salt, which are able to afford high levels of asymmetric induction in formation of the alkylated product. Once it was established that the most efficient ligands for this reaction, both in terms of activity and enantioselectivity, are phosphorus(III) species such as phosphites and phosphoramidites, a great deal of efforts has been addressed towards the design of such ligands, especially those having the most suitable stereochemical features that allow a high level of asymmetric induction to be reached.[2] Recently, the diastereoisomeric control of *tropos* ligands combined with a chiral subunit which adopts a preferential conformation of a diastereoisomeric complex,[3] has allowed us to obtain phosphite and phosphoramidite ligands based on a chiral unit and a *tropos* biphenol moiety that have proven able to induce high enantioselectivities in the copper catalyzed conjugate addition of dialkylzinc reagents.[4] Their success lies in the capability of the configurationally stable unit to induce a prevalent screw sense in the flexible moiety: this guarantees the presence of a greatly prevalent diastereoisomer, which must give rise to the formation of a very enantioselective catalyst,[3a] and hence the achievement of high ees.

Very recently, we have demonstrated that the cholestanic moiety represents a configurationally stable unit capable of exerting an excellent diastereoisomeric control on the *tropos* biphenylphosphite framework in the preparation of bile acid derived biphenylphosphites.[5] The diastereoisomeric control depends on the position of the cholestanic backbone where the biphenylphosphite moiety is linked: as a matter of fact, the biphenylphosphite moiety linked at the 12-position, as in phosphite **1**, shows a very high prevalence of the M torsion.[5] By contrast, the biphenylphosphite unit adopts a prevalent P screw sense when linked at the 7-position of cholic acid, and the phosphite bearing the same moiety at the 3-position of the cholestanic skeleton exists as an equimolar mixture of two rapidly interconverting M–P diastereoisomers.[5] The good asymmetric induction exerted by the cholestanic skeleton on the *tropos* biphenylphosphite moiety linked at the 7- and 12-positions suggests that they can be used as chiral controllers in the asymmetric copper catalyzed conjugate addition of diethylzinc to enones. In addition, given the

* Corresponding author. Fax: +39 0509 18260; e-mail: iuliano@dcci.unipi.it

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tropos nature of the bile acid derived biphenylphosphites, the ligand bearing the biphenylphosphite moiety at the 3-position can give rise to the formation of a prevailing diastereoisomeric species when the copper complex is formed. However, preliminary results concerning the use of these phosphites as chiral ligands in the copper catalyzed conjugate addition of diethylzinc to enones showed that only **1** is able to afford asymmetric induction in this reaction.[6] These results prompted us to address our efforts only towards the use, as chiral controllers, of **1** and other kind of deoxycholic acid derived phosphites, bearing the phosphite moiety at the 12-position. Since it is well known that substitution on the biphenyl framework can affect the efficiency of a *tropos* ligand,[7] we were interested in checking the effect of the presence of substituent groups at the 5,5′-positions of the biphenyl system on the stereochemical features of this type of ligands as well as on the outcome of the alkylation reaction.

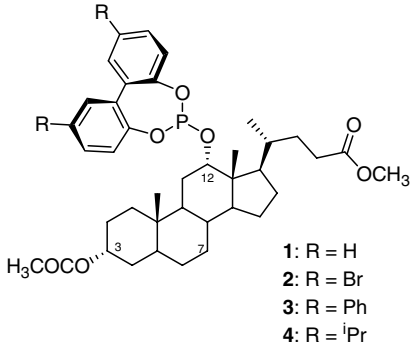


Figure 1. Structures of the phosphites.

Herein we report the synthesis and stereochemical characterization of phosphites **2**–**4** (Fig. 1), where a 5,5′-substituted biphenylphosphite moiety is linked at the 12-position of the cholestanic backbone, and the results obtained using phosphites **1**–**4** as chiral ligands in the asymmetric copper catalyzed conjugate addition of diethylzinc to acyclic enones.

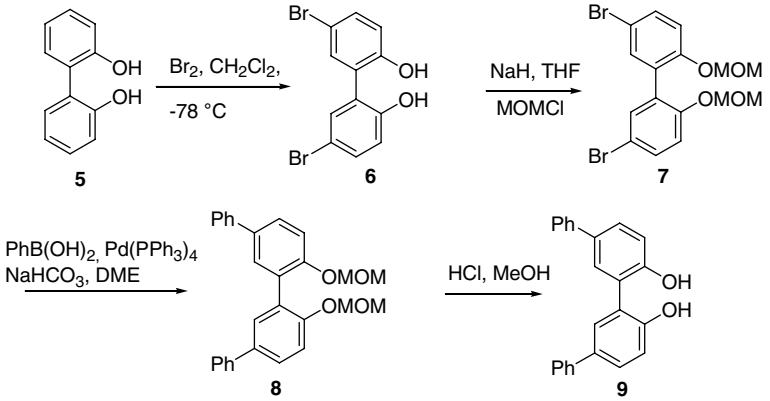
2. Results and discussion

2.1. Synthesis of phosphites 2–4

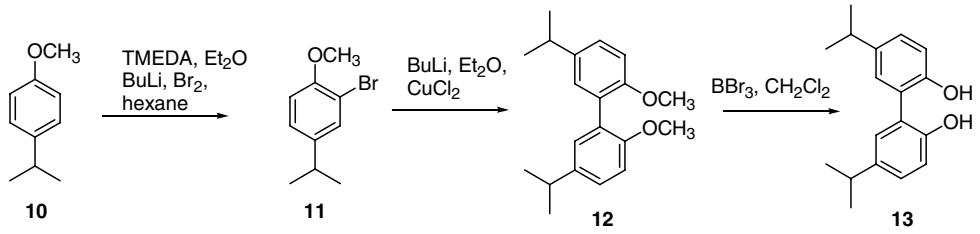
Biphenols **6** and **9**, which constitute the flexible part of phosphites **2** and **3**, respectively, were prepared as reported in Scheme 1, according to a modification of a synthetic method used to prepare the analogous 3,3′,5,5′-tetrasubstituted biphenols.[7]

Bromination of the 5,5′-positions was realized in 65% yield, by reacting biphenol **5** with a slight excess of bromine in dichloromethane solution at low temperature; reaction conditions that promote the formation of the kinetic product.[8] Biphenol **6** was used as starting material for the preparation of **9**, which was obtained in 65% overall yield from **6** by the protection of the OH groups, Suzuki coupling[9] with phenylboronic acid and acidolysis of the methoxymethyl protecting groups.

The synthetic route to biphenol **13**, the precursor of phosphite **4**, is outlined in Scheme 2 and follows a literature method.[10]



Scheme 1. Synthesis of 5,5′-diphenyl-2,2′-dihydroxybiphenyl.



Scheme 2. Synthesis of 5,5′-diisopropyl-2,2′-dihydroxybiphenyl.

According to this procedure, commercial 4-isopropylanisole **10** was *ortho*-metallated by butyllithium and TMEDA and the resulting lithium derivative was treated with bromine, to afford **11**, which was used without purification in the coupling reaction. The copper promoted coupling of **11** afforded **12** in 45% yield, after chromatographic purification. Deprotection of the OH groups with BBr_3, gave biphenol **13** in 50% yield.

Phosphites **2**–**4** were obtained by reacting the deoxycholic acid derivative **14** with the suitable biphenylchlorophosphite in the presence of triethylamine and DMAP (Scheme 3). To achieve satisfactory yields of these phosphites, a slight modification of the previous preparation was mandatory: the chlorophosphite prepared at room temperature, instead of at −60 °C, was reacted with **14** in the presence of a large excess of triethylamine and a stoichiometric amount of DMAP.[11]

2.2. Stereochemical characterization

The stereochemical features of phosphites **2**–**4**, that is, the sense of twist of the substituted biphenyl moiety and the extent of its prevalence and *tropos* nature, were assayed by CD and NMR spectroscopy. CD spectroscopy is the most suitable way to determine if the substituted biphenyl moiety is twisted in a prevalent screw sense in phosphites **2**–**4**. In fact, the only absorbing chromophore in the wavelength region between 300 and 230 nm is the substituted biphenyl moiety[12] and Cotton effects in this region can be present only if this moiety, linked to the bile acid system, is twisted in a prevalent screw sense.[12] In addition, a correlation between the sign of the CD bands of **1** and the sense of twist of the biphenyl moiety has been established,[5] so that a comparison of the CD spectra of these phosphites with that of **1** can allow us to determine the prevalent sense of twist of the biphenyl unit. The CD spectra of **2** and **4** can be compared safely with the CD spectrum of **1**, given that the presence of bromine or isopropyl groups at the 5,5′-positions of the biphenylphosphite moiety does not modify the nature of the chromophore to a significant extent.[13] This is confirmed by the high similarity of the UV spectra of **2**, **4** (Figs. 2 and 3) and **1**, as far as number, position and sign of the bands are concerned.

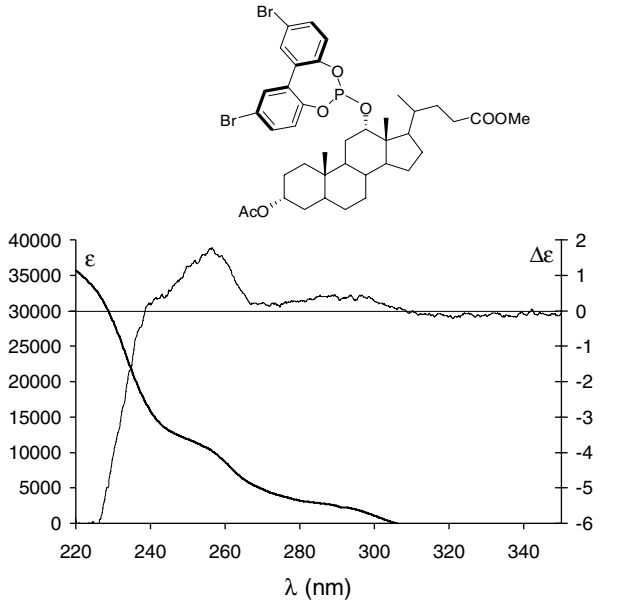


Figure 2. Absorption (bold line) and CD (solid line) spectra of **2** in ACN.

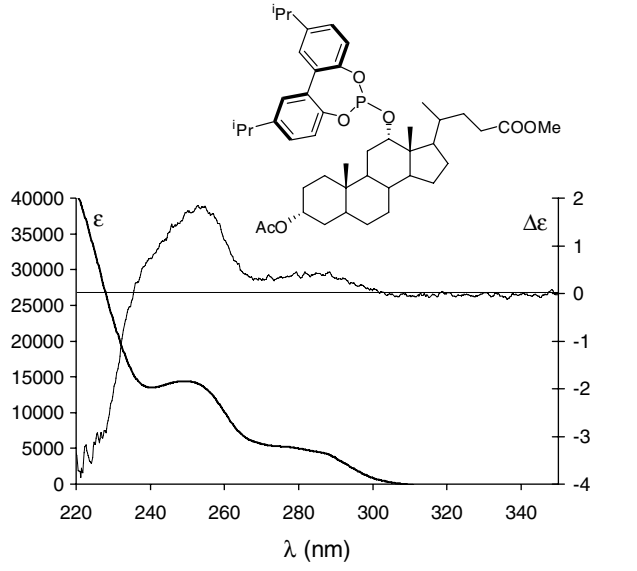
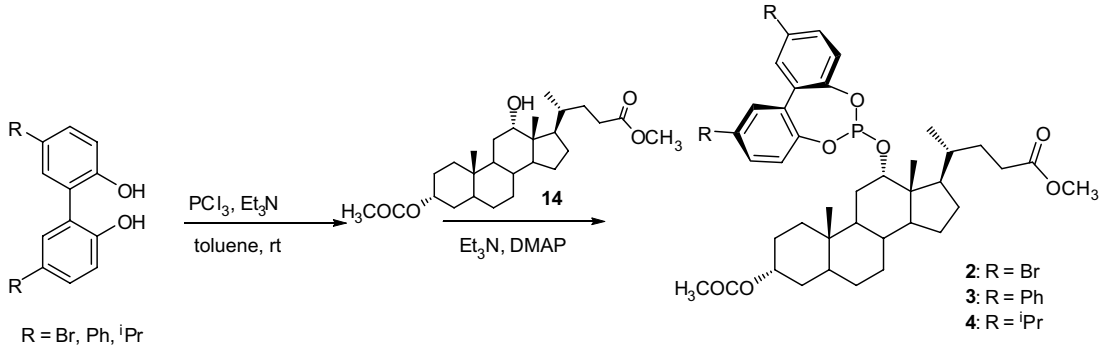


Figure 3. Absorption (bold line) and CD (solid line) spectra **4** in ACN.



Scheme 3. Synthesis of phosphites **2**–**4**.

The CD spectrum of **2** (Fig. 2), which shows two positive Cotton effects at 290 nm ($\Delta\varepsilon$ 0.4) and at 255 nm ($\Delta\varepsilon$ 1.7), and that of **4** (Fig. 3), showing two positive Cotton effects at 285 nm ($\Delta\varepsilon$ 0.4) and at 252 nm ($\Delta\varepsilon$ 1.8), are similar to the CD spectrum[5] of **1**, as far as the number and sign of the Cotton effects are concerned. The presence of Cotton effects in the CD spectra of **2** and **4** suggests that the substituted biphenyl moiety of these phosphites is twisted in a prevalent screw sense.[12] By comparing the CD spectra of **2** and **4** to that of **1**, based on the sign of the Cotton effects, a prevalence of M torsion for the substituted biphenyl moieties of **2** and **4** is inferred. The lower intensity of the CD bands in both spectra with respect to that of the Cotton effects in the CD spectrum of **1**, is attributable to a lower prevalence of the M screw sense in the case of **2** and **4**. The extent of the prevalence can be evaluated as 39% in the case of **2** and 42% in the case of **4**, using a value of 4.3 ($\Delta\varepsilon$ of the CD band at 250 nm in the CD spectrum of **1**)[5] as $\Delta\varepsilon_{max}$ and assuming that the dihedral angle between the aromatic rings of the biphenyl moieties of **1**, **2** and **4** is almost the same.

All of these considerations cannot be applied to phosphite **3**, where the two conjugated phenyl rings at the 5,5′-positions make this substituted biphenylphosphite moiety a completely different chromophore.[13] As a matter of fact, the UV spectrum of **3** (Fig. 4) only shows one absorbing band, very large, centered at 250 nm (ε 75,000), which is very different with respect to the UV spectrum of **1**. The CD spectrum (Fig. 4) shows a negative Cotton effect at 270 nm ($\Delta\varepsilon$ −5), suggesting that the 5,5′-diphenylbiphenylphosphite unit also assumes a prevalent screw sense. However, given that the chromophores of **1** and **3** are different, the comparison between their CD spectra cannot be used to assess the sense of twist of the substituted biphenyl moiety of **3**, which must be determined otherwise.

To verify if in the case of phosphites **2**–**4** dependence of the sense of twist on the solvent exists as in the case of **1**,[5] CD measurements in THF solutions were performed. The CD spectra of **2** and **4** (Fig. 5) recorded in THF solution show

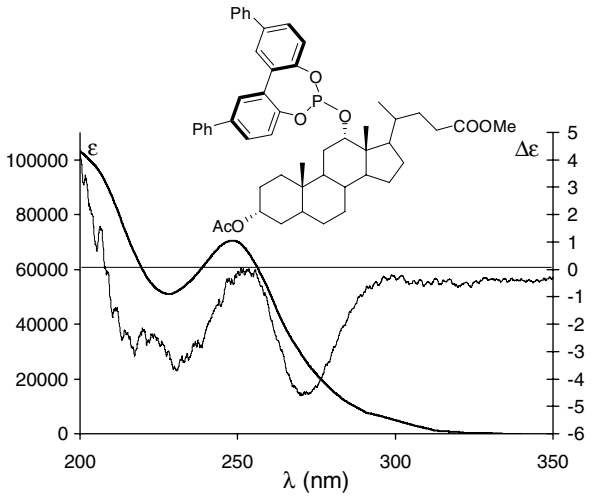


Figure 4. Absorption (bold line) and CD (solid line) spectra **3** in ACN.

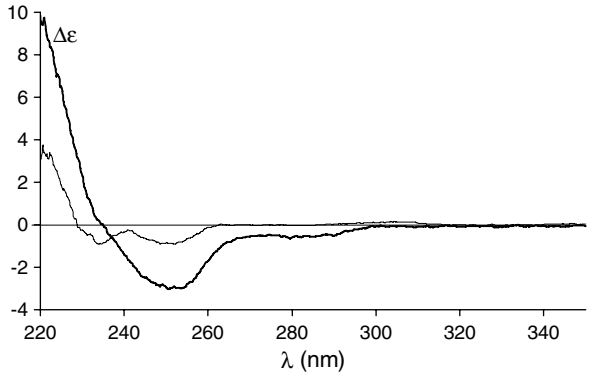


Figure 5. CD spectra of phosphites **2** (solid line) and **4** (bold line) in THF.

the presence of two negative Cotton effects, at 280 and 250 nm, symptomatic of the prevalence of a P screw sense.

As observed in the case of **1**, the CD bands of **2** in THF are less intense ($\Delta\varepsilon$ −0.9 at 250 nm) than the corresponding CD bands in ACN solution, indicating a lower prevalence of the P sense of twist. On the contrary, the intensity of the Cotton effects in the CD spectrum of **4** in THF is higher ($\Delta\varepsilon$ −3.0 at 250 nm) than in ACN, suggesting that in this case, the prevalence of the P screw sense in THF solution is higher than the prevalence of the M sense of twist in ACN solution. In the case of **3**, disappearance of the CD signal is observed in passing from the ACN solution to the THF solution.

The dependence of the sense of twist on the solvent points at the *tropos* nature of the phosphites **2**–**4** and hence variable temperature ^{31}P NMR measurements were carried out to determine the M–P interconversion barrier as well as the ratio of the two diastereisomeric forms. The measurements were performed in THF-d_8 and toluene-d_8.[14] The variable temperature ^{31}P NMR measurements show a very similar behaviour of the three phosphites.

The variable temperature profile of the ^{31}P NMR spectra in toluene-d_8 (Fig. 6) and THF-d_8 (Fig. 7) of **4**, chosen as an example, confirms the hypothesis coming from the CD measurements about the presence at room temperature of two rapidly interconverting M–P diastereoisomeric species. As a matter of fact, only one signal at 155.6 ppm is present

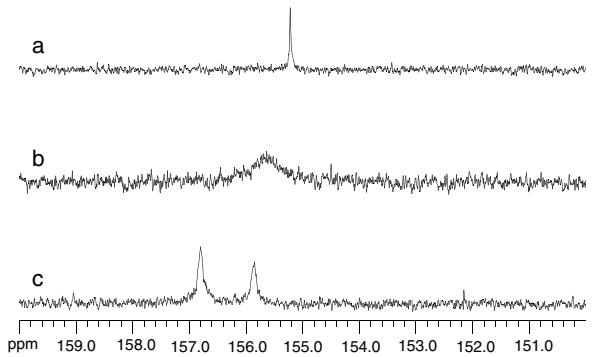


Figure 6. ^{31}P NMR (121 MHz, toluene-d_8) spectra of phosphite **4** at 25 °C (a), −40 °C (b) and −60 °C (c).

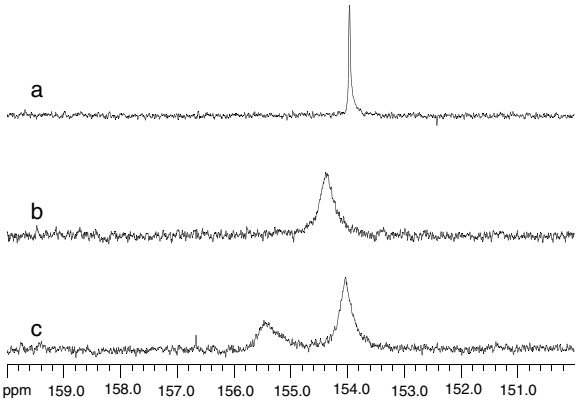


Figure 7. ^{31}P NMR (121 MHz, THF-d_8) spectra of phosphite **4** at 25 °C (a), −40 °C (b) and −60 °C (c).

in the spectrum recorded in toluene solution at room temperature (Fig. 6), which broadens at −40 °C and splits at −60 °C in two baseline separated signals at 155.8 and 156.8 ppm, the integrated areas of which give a diastereomeric ratio of 25% in favour of the M diastereoisomer[15] that resonates at higher frequencies. The spectroscopic pattern in THF solution (Fig. 7) is similar: the signal present at room temperature at 154.0 ppm broadens at −40 °C and splits in two resonances (154.0 ppm and 155.4 ppm) at −60 °C. The integrated areas of the two signals give a diastereomeric ratio of 48% in favour of the P diastereoisomer that resonates at lower frequencies. These NMR data are in keeping with the CD results discussed above, which showed a higher prevalence of the P diastereoisomer in THF solution than the M diastereoisomer in ACN solution.

This variable temperature behaviour is the same for phosphites **2** and **3**, the sole exception being the decoalescence temperature of **2** in toluene solution, which is −80 °C. It is noteworthy that, at the decoalescence temperature, the M diastereoisomer resonates at higher frequencies for both **2** and **4**, and **3** shows the same spectroscopic pattern (Fig. 8): on this basis, it is also possible to determine the prevalent sense of twist for phosphite **3** that results, as in the other cases, M in toluene and P in THF solution. The integrated areas of the signals at the decoalescence temperature show a prevalence of the M diastereoisomer in toluene solution of 22% for **2**, and a prevalence of the P diastereoisomer in THF solution of 13% for **2** and 16% for **3**. The interconversion barriers, evaluated on the basis of the variable temperature NMR measurements,[16] are in the range 10.70–10.85 kcal/mol for all the phosphites in both the solvent: only phosphite **2** shows a lower barrier (9.93 kcal/mol in toluene solution and 10.30 kcal/mol in THF solution).

2.3. Conjugate addition of diethylzinc to acyclic enones

Phosphites **1**–**4** were assayed as chiral auxiliaries in the copper catalyzed conjugate addition of diethylzinc to acyclic enones. In a typical procedure, the catalytic system was generated in situ by reacting a solution of the copper salt and the chiral ligand for 1 h at room temperature, followed

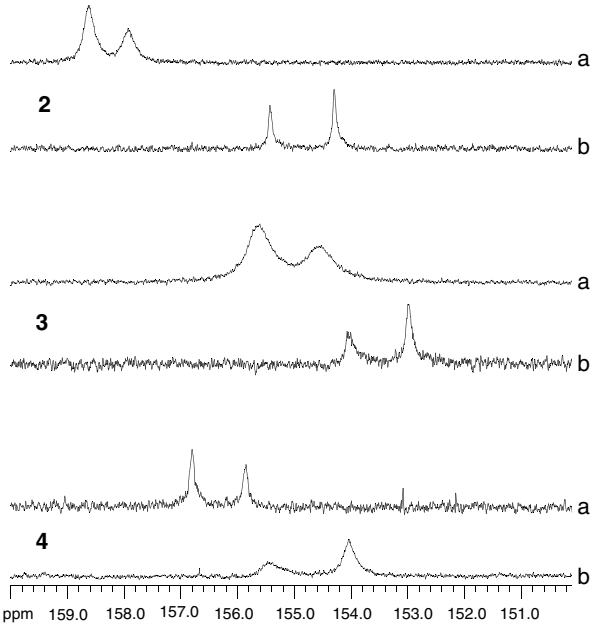
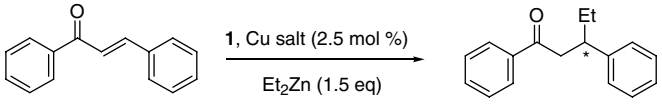


Figure 8. ^{31}P NMR (121 MHz) spectra of phosphites **2**–**4** in toluene (a) and THF (b) at the decoalescence temperature.

by the addition of diethylzinc. The effect of different parameters on the outcome of the reaction was checked using phosphite **1** as a chiral controller and chalcone as a substrate: Table 1 reports on the obtained results.

All reactions were monitored by TLC and stopped when the conversion of the substrate was complete or did not proceed further. The catalytic system generated by mixing $Cu(OTf)_2$ and **1** in molar ratio of 1:1.2, affords, in toluene solution at 0 °C, the alkylated product in quantitative yield and 26% ee, after 2 h (entry 1). Lowering the reaction temperature to −20 °C improves the enantioselectivity of the conjugate addition (entry 2), without altering the reaction rate. Higher asymmetric induction is reached by performing the reaction at −50 and −70 °C (entries 3 and 4), but, at these temperatures, longer reaction times are required to obtain a satisfactory yield of the alkylation product. Increasing of the amount of chiral ligand accelerates the reaction, which affords a quantitative yield of the product at −50 °C after 2 h (entry 5); by contrast, under these conditions, the enantioselectivity decreases slightly. Changing the solvent gives rise to lower ees (entries 6–8) and, in some cases (entries 7 and 8) also to lower yields, because of the formation of a by-product coming from the attack of the in situ formed enolate to another molecule of unreacted substrate.[17] The prevailing enantiomer is (*S*)-configured, except when THF is used as the reaction solvent. It is known that in deoxycholic acid-based binaphthylphosphites the absolute configuration of the alkylated product depends only on the absolute configuration of the binaphthyl moiety.[18] Given that the sense of twist of the biphenyl moiety of **1**, which corresponds to the absolute configuration of the binaphthyl moiety, changes in passing from toluene to THF, the change of the sense of asymmetric induction (entries 3 and 7) has to be attributed to inversion of the screw sense. In addition, it is noteworthy

Table 1. Catalytic enantioselective conjugate addition to chalcone in the presence of **1**



Entry	Cu Salt	**1** (mol %)	Time (h)	Solvent	Temperature (°C)	Yield[a] (%)	ee[b] (%)	AC[c]
1	$Cu(OTf)_2$	3.0	2	Toluene	0	100	26	*S*
2	$Cu(OTf)_2$	3.0	2	Toluene	−20	100	34	*S*
3	$Cu(OTf)_2$	3.0	5	Toluene	−50	72	43	*S*
4	$Cu(OTf)_2$	3.0	7	Toluene	−70	89	44	*S*
5	$Cu(OTf)_2$	6.0	2	Toluene	−50	100	39	*S*
6	$Cu(OTf)_2$	3.0	4	Et_2O	−50	85	26	*S*
7	$Cu(OTf)_2$	3.0	5	THF	−50	55	35	*R*
8	$Cu(OTf)_2$	3.0	7	CH_2Cl_2	−50	25	—	—
9	$Cu(OAc)_2 \cdot H_2O$	3.0	6	Toluene	−70	24	17	*S*

[a] Determined by NMR.
[b] Determined by HPLC analyses on Chiralcel OJ, 254 nm, 1.0 mL/min, hexane–2-propanol 99.5:0.5.
[c] Determined by comparison with an enantiomerically enriched sample of known configuration.[18]

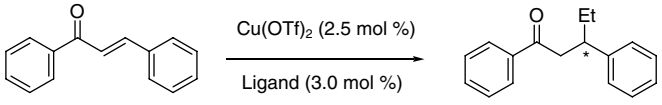
that the sense of asymmetric induction remains the same in going from deoxycholic acid-based binaphthylphosphite to **1**: in fact, the phosphite possessing the (*R*)-binaphthyl moiety, corresponding to an M screw sense of the biphenyl unit, afforded an (*S*)-configured alkylation product,[18] as observed in the case of **1**. The use of a different copper salt (entry 9) gives worse results both in terms of yield and enantioselectivity of the reaction.

Taking into account these results, for comparative purposes, the other phosphites were checked as chiral ligands in the copper catalyzed conjugate addition of diethylzinc to chalcone under the optimal reaction conditions, that is, ligand to copper salt ratio 1.2:1, $Cu(OTF)_2$ as copper salt, temperature of −50 °C and toluene and THF as solvents. Table 2 lists the results obtained.

A study of Table 2 shows that substitution at the 5,5′-position of the biphenyl moiety affords 12-deoxycholic acid derived biphenylphosphites able to give a more efficient catalytic system with respect to **1**: not only does the conjugate addition, in toluene as a solvent, proceed faster but also the ees of the alkylation product are slightly higher (entries 3, 5 and 8).

Lowering of the temperature to −70 °C caused a slight improvement of the ee of the alkylation product only in the case of phosphite **3** (entry 6); by contrast, under these reaction conditions, the catalytic system generated by **4**, which at −50 °C affords the best asymmetric induction, gives lower enantioselectivity (entry 9). The prevailing enantiomer is (*S*)-configured when the reaction is carried out in toluene solution (entries 1, 3, 5, 6, 8 and 9) and (*R*)-configured for the reactions performed in THF (entries 2, 4, 7 and 10). Given that the prevalent sense of twist of the biphenyl moiety of phosphites **2**–**4** is opposite in these two solvents, again the absolute configuration of the alkylated product depends only on the configuration of the biaryl unit of the phosphites. THF is a worse reaction solvent with respect to toluene, affording lower yields in longer reaction times (entries 2, 4 and 7), except when **4** is used as chiral ligand (entry 10). The trend of the ees in THF

Table 2. Catalytic enantioselective conjugate addition to chalcone



Entry	Ligand	Time[a] (h)	Solvent	Temperature (°C)	Yield[a] (%)	ee[b] (%)	AC[c]
1	**1**	5	Toluene	−50	72	43	*S*
2	**1**	5	THF	−50	55	35	*R*
3	**2**	3	Toluene	−50	100	45	*S*
4	**2**	3	THF	−50	35	10	*R*
5	**3**	2.5	Toluene	−50	100	47	*S*
6	**3**	4	Toluene	−70	94	50	*S*
7	**3**	7	THF	−50	28	12	*R*
8	**4**	6	Toluene	−50	100	51	*S*
9	**4**	6.5	Toluene	−70	100	38	*S*
10	**4**	6	THF	−50	70	65	*R*

[a] Determined by NMR.
[b] Determined by HPLC analyses on Chiralcel OJ, 254 nm, 1.0 mL/min, hexane–2-propanol 99.5:0.5.
[c] Determined by comparison with an enantiomerically enriched sample of known configuration.[18]

vs toluene reflects the extent of the prevalence of the screw sense of biphenylphosphite unit, which is higher in toluene than in THF for **2** and **3**, but lower for **4**. As a matter of fact, very low asymmetric induction was obtained when using **2** and **3** as ligands in THF solution (entries 4 and 7), whereas performing the reaction with **4** in THF gave the highest ee (entry 10). The results obtained in toluene and in THF seem conflicting, given the complete prevalence, in toluene, of the M sense of twist in the case of **1** and a lower prevalence for the other phosphites, which in spite of this give better enantioselectivity. This behaviour can be explained[19] allowing for the formation of a highly prevalent diastereisomeric species, in toluene solution, once the catalytically active copper complex is formed, in the case of phosphites **2**–**4**.

This should be possible as the alkylation reactions are carried out near the decoalescence temperature,[20] where the equilibrium between the two species is still rapid: this mechanism seems operating specially in the case of **4**, which gives a decrease in the ee of the alkylation product when lowering the reaction temperature under −50 °C. Alternatively, it is also conceivable that one of the two diastereomeric complexes has higher activity and, hence, determines the outcome of the reaction.[3a]

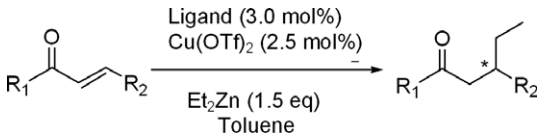
Screening of phosphites **1**–**4** as chiral ligands in the copper catalyzed conjugate addition of diethylzinc to chalcone has showed that phosphites **3** and **4** are the best ligands at temperatures of −70 and −50 °C, respectively. To check the effect of the substrate structure on the outcome of the reactions promoted by **3** and **4**, different acyclic enones were screened with the results reported in Table 3.

Changing of the substrate requires longer reaction times to obtain satisfactory yields of the alkylation products with both the phosphites. The presence of an electron rich aromatic ring linked to the carbonyl group reduces the enantioselectivity of the reaction promoted by **3**, independent of the structure of the aromatic unit (entries 2 and 5). On the contrary, the asymmetric induction exerted by **3** increases with a substrate possessing an electron rich aromatic ring linked to the olefinic carbon atom (entry 3). This result is perfectly in keeping with the lower ee obtained in the conjugate addition of diethylzinc to the enone bearing an electron poor *p*-chlorophenyl group linked to the olefinic carbon (entry 4). As far as phosphite **4** is concerned, electronic factors seem to have less importance than structural factors: as a matter of fact, the two substrates having an electron rich aromatic ring linked to the carbonyl group afford different ees (entries 7 and 10). In contrast, chalcone and the two enones bearing the electron rich aromatic ring linked at the carbonyl group or at the olefinic carbon atom are alkylated with comparable ees (entries 6–8). The presence of an electron poor aromatic ring is detrimental to the reaction promoted by **4**, which affords the alkylation product in only 32% ee (entry 9).

3. Conclusions

The synthesis of deoxycholic acid derived phosphites bearing a 5,5′ substituted biphenylphosphite moiety linked at the 12-position of the cholestanic backbone has allowed us to obtain *tropos* systems, showing stereochemical properties that depend on the type of substituent. CD analysis showed that the substitution at the 5,5′-position of the biphenyl unit does not prevent the capability of the cholestanic moiety to induce a prevalent sense of twist to the biphenylphosphite framework linked at its 12-position. However, the presence of substituents at these positions affects the extent of the prevalence of the screw sense, which is lower than in the case of the analogous biphenylphosphite devoid of substituents. The *tropos* nature of phosphites **2**–**4** joined to a low interconversion barrier of their biphenyl moiety engenders the change of the sense of twist in passing from toluene and ACN to THF. The nature of the substituents at the 5,5′-position affects the M–P diastereoisomeric ratio, whereas the kinetics of the interconver-

Table 3. Catalytic enantioselective conjugate addition to acyclic enones



Entry	Ligand	R_1	R_2	Temperature (°C)	Time (h)	Yield[a] (%)	ee[b] (%)
1	**3**	Ph	Ph	−70	3	75	50
2	**3**	*p*-OMe(C_6H_4)	Ph	−70	6	51	40
3	**3**	Ph	*p*-OMe(C_6H_4)	−70	6	59	60
4	**3**	Ph	*p*-Cl(C_6H_4)	−70	6	55	41
5	**3**	2-Thienyl	Ph	−70	6	22	40[c]
6	**4**	Ph	Ph	−50	6	100	51
7	**4**	*p*-OMe(C_6H_4)	Ph	−50	7	80	50
8	**4**	Ph	*p*-OMe(C_6H_4)	−50	7	52	46
9	**4**	Ph	*p*-Cl(C_6H_4)	−50	7	29	32
10	**4**	2-Thienyl	Ph	−50	7	50	40[c]

[a] Determined by NMR.
[b] Determined by HPLC analyses on Chiralcel OJ, 254 nm, 1.0 mL/min, hexane–2-propanol 99.5:0.5.
[c] Determined by HPLC analyses on Chiralcel OD-H, 254 nm, 1.0 mL/min, hexane–2-propanol 99.75:0.25.

sion is very similar for the three phosphites. Only **2** exhibits a slightly faster interconversion kinetics.

The use of phosphites **1**–**4** as chiral ligands in the copper catalyzed conjugate addition of diethylzinc to acyclic enones gives rise to catalysts able to promote the alkylation reaction in an enantioselective fashion. The extent of the asymmetric induction depends on the structure of the phosphite as well as the reaction conditions. Because of their *tropos* nature, the enantioselection, in toluene solution, does not depend on the extent of the prevalence of the screw sense of the substituted biphenyl unit of **2**–**4**. In contrast, when THF is used as a reaction solvent, the extent of the enantioselectivity can be related to the prevalence of the sense of twist in this solvent. The sense of asymmetric induction depends only on the sense of twist of the biphenyl moiety of phosphites **1**–**4**: actually, the inversion of the sense of twist in THF corresponds to the achievement of an alkylation product having an opposite absolute configuration. This is an interesting result, especially as far as the use of **4** as a chiral ligand is concerned. In fact, given that a satisfactory yield of the alkylation product is obtained using this ligand in THF as a solvent, it is possible to obtain both enantiomers of the alkylation product starting from the same chiral ligand, by only changing the reaction solvent. Finally, considering that the substitution on the biphenyl moiety of 12-substituted deoxycholic acid based biphenylphosphites affects the outcome of the copper catalyzed conjugate addition of diethylzinc to acyclic enones, it is conceivable that even better results could be obtained by changing both the nature and position of the substituents: studies are currently in progress to this end.

4. Experimental

4.1. General procedures and material

TLC analyses were performed on silica gel 60 sheets; flash chromatography separations were carried out on columns using silica gel 60 (230–400 mesh). Toluene and was refluxed over sodium and distilled before the use. THF and diethylether were refluxed over Na/K alloy and distilled before use. Triethylamine and TMEDA were refluxed over CaH_2 and distilled before use. Methoxymethyl chloride, 1,2-dimethoxyethane and PCl_3 were distilled before the use. Unless otherwise specified, the reagents were used without any purification. Methyl 3α-acetyloxy-12α-hydroxy-5β-cholan-24-oate **14**[21] and the substituted unsaturated ketones[22] were obtained as previously described and matched the reported characteristics.[18]

4.2. Instrumentation

^{1}H NMR spectra were recorded in $CDCl_3$, benzene-d_6 or DMSO-d_6 on a 200 MHz NMR spectrometer or a 300 MHz NMR spectrometer. The following abbreviation are used: s = singlet, d = doublet, dd = double doublet, t = triplet, hept = heptet, m = multiplet, br = broad. ^{13}C NMR were recorded at 50 MHz. The temperature was controlled to ±0.1 °C. ^{1}H and ^{13}C NMR chemical shifts are referenced to TMS as external standard. ^{31}P NMR spectra were recorded in toluene-d_8 or THF-d_8 at 121 MHz: ppm are referred to H_3PO_4 as external standard. IR stretches are given in cm^{-1}. Circular dichroic (CD) spectra were obtained using a 0.1-cm path length cell and spectropolarimetric grade acetonitrile or THF as solvents, at 25 °C, unless otherwise specified. Sample concentration for CD analyses was typically $(6–9) \times 10^{-4}$ M. UV–vis absorption spectra were obtained using a 0.1-cm path length cell and spectrophotometric grade acetonitrile or THF as solvents, at 25 °C. Sample concentration of UV–vis analyses was typically $(6–9) \times 10^{-4}$ M. Optical rotations were measured with a digital polarimeter. Melting points are uncorrected.

4.2.1. 5,5′-Dibromo-2,2′-dihydroxybiphenyl 6. Bromine (2.8 mL, 56.04 mmol) was slowly added to a solution of **5** (3.91 g, 20.98 mmol) in CH_2Cl_2 (120 mL) at −75 °C. The solution was stirred at room temperature and a solution of 10% $NaHSO_3$ was added after 3 h; the precipitate was filtered and dissolved in ethyl acetate. The organic layer was washed with a solution of 10% $NaHSO_3$, brine and dried over anhydrous Na_2SO_4. After removing the solvent in vacuo, **6** was obtained as a brown solid (4.5 g, 63%). ^{1}H NMR (300 MHz, DMSO-d_6, δ): 6.93 (d, $J = 8$ Hz, 1H); 7.33–7.39 (dd, $J_1 = 8$ Hz, $J_2 = 2.4$ Hz, 2-H). ^{13}C NMR (75 MHz, DMSO-d_6, δ): 110.2; 118.4; 127.2; 131.7; 134.1; 154.7. Anal. Calcd for $C_{12}H_8Br_2O_2$: C, 41.90; H, 2.34; Br, 46.46; O, 9.30. Found: C, 41.85; H, 2.36; Br, 46.49.

4.2.2. 5,5′-Dibromo-2,2′-bis(methoxymethyloxy)biphenyl 7. A solution of **6** (4 g, 11.6 mmol) in dry THF (40 mL) was slowly added, under nitrogen, to a suspension of NaH (0.835 g, 34.88 mmol) in dry THF (150 mL). A solution of methoxymethyl chloride (2.7 mL, 34.88 mmol) in dry THF (20 mL) was added to the mixture after 2 h. The resulting suspension was stirred overnight under nitrogen, and water was then added to quench the reaction. The organic layer was washed with an aqueous solution of 10% $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. After removing the solvent in vacuo and recrystallization from CH_2Cl_2, pure **7** was obtained (4.06 g, 81%) mp = 122–123 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 3.35 (s, 3H); 5.06 (s, 2H); 7.1 (d, $J = 9$ Hz, 1H); 7.35 (d, $J = 2.4$ Hz, 1H); 7.42 (dd, $J_1 = 8.7$ Hz, $J_2 = 2.4$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 53.2; 98.0; 115.9; 116.8; 124.4; 131.7; 133.9; 159.9. IR (KBr, cm^{-1}): 2957; 2361; 2343; 1772; 1734; 1718; 1700; 1684; 1670; 1654; 1647; 1636; 1576; 1560; 1540; 1507; 1490; 1448; 1399; 1309; 1261; 1224; 1199; 1165; 1135; 1089; 990; 922; 874; 820. Anal. Calcd for $C_{16}H_{16}Br_2O_4$: C, 44.47; H, 3.73; Br, 36.98; O, 14.81. Found: C, 44.51; H, 3.72; Br, 37.01.

4.2.3. 5,5′-Diphenyl-2,2′-bis(methoxymethyloxy)biphenyl 8. $Pd(PPh_3)_4$ (0.27 g, 0.23 mmol) was added under nitrogen to a solution of **7** (1 g, 2.13 mmol) in 1,2-dimethoxyethane (70 mL). The mixture was stirred at room temperature until the palladium complex was dissolved, and then of a $NaHCO_3$ 1 M solution (20 mL) was added. After 30 min of stirring, phenylboronic acid (1.13 g, 9.24 mmol) was added. The mixture was stirred over 70 h under nitrogen at room temperature and was then heated to 100 °C over 24 h. The resulting brown mixture was

allowed to cool to room temperature and then was filtered through a Celite pad. The solvent was evaporated in vacuo, and the product was dissolved in ethyl acetate. The organic layer was washed with water, 10% NaOH, 10% HCl, 10% $NaHCO_3$ and brine in that order then dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo followed by chromatographic purification (CH_2Cl_2/acetone, 80:20) yielded 0.73 g (1.71 mmol, 80%) of pure **8**. ^1H NMR (300 MHz, $CDCl_3$, δ): 3.39 (s, 3H); 5.15 (s, 2H); 7.29–7.45 (m, 4H); 7.57–7.63 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 56.2; 95.5; 116.1; 127.1; 127.6; 129.0; 129.6; 130.5; 135.1; 140.9; 154.8. IR (KBr, cm^{-1}): 3030; 2954; 2899; 2847; 2824; 2786; 1602; 1508; 1479; 1449; 1398; 1307; 1270; 1233; 1198; 1155; 1143; 1131; 1078; 1050; 1001; 921; 893; 872; 822. Anal. Calcd for $C_{28}H_{26}O_4$: C, 78.85; H, 6.14; O, 15.01. Found: C, 78.79; H, 6.18.

4.2.4. 5,5′-Diphenyl-2,2′-dihydroxybiphenyl 9. A suspension of **8** (670 mg, 1.57 mmol) in methanol (95 mL) was heated to 65 °C under a nitrogen atmosphere and concentrated hydrochloric acid (0.63 mL) was then added. After 2 h of stirring under these conditions, the mixture was cooled to room temperature and a solution of 10% $NaHCO_3$ was added until CO_2 evolution ceased. The methanol was evaporated in vacuo and the residue was dissolved in ethyl acetate, washed with a solution of $NaHCO_3$ and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave pure **9** as a white solid (0.5 g, 1.48 mmol, 94%). Mp = 182–184 °C. ^1H NMR (300 MHz, $CDCl_3$, δ): 7.15 (d, $J = 8.1$ Hz, 1H); 7.33 (t, $J = 7.2$ Hz, 1H); 7.43 (t, $J = 7.1$ Hz, 2H); 7.58–7.63 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 117.4; 124.1; 127.0; 127.3; 129.0; 129.1; 130.2; 135.2; 140.5; 152.7. Anal. Calcd for $C_{24}H_{18}O_2$: C, 85.18; H, 5.36; O, 9.46. Found: C, 85.22; H, 5.33.

4.2.5. 2-Bromo-4-isopropylanisole 11. A 2.5 M solution of BuLi in hexane (53.5 mL) was added dropwise to a solution of **10** (10 g, 66.6 mmol) and 20 mL (0.13 mol) of TMEDA in ethyl ether (75 mL). After 2 h, the mixture was cooled to −78 °C and a solution of bromine (7 mL, 0.14 mol) in hexane (15 mL) added dropwise. The reaction mixture was allowed to warm to room temperature, then 50 mL of 3 M HCl were added and the aqueous phase extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4. After removing the solvent in vacuo, crude **11** was obtained as a colourless oil (14.4 g) and used without further purification.

4.2.6. 2,2′-Dimethoxy-5,5′-diisopropylbiphenyl 12. A solution of 2.5 M BuLi in hexane (30 mL) was cooled to −78 °C and a solution of 14.4 g (62.8 mmol) **11** in dry ethyl ether (68.3 mL) was slowly added. After the addition was complete, the reaction mixture was allowed to warm to rt over 1 h, then cooled again to −78 °C. Under intensive stirring, 17 g of $CuCl_2$ was added portionwise. The resultant mixture was stirred at this temperature for 2 h and then allowed to warm to rt. The reaction mixture was quenched with H_2O (30 mL) and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated at reduced pressure to give an oily residue. The crude product was purified by flash chromatography (CH_2Cl_2–hexane 30:70), affording pure **12** as an oil (8.4 g, 28.3 mmol, 45%). ^1H NMR (300 MHz, $CDCl_3$, δ): 1.29 (d, $J = 6.9$ Hz, 6H); 2.93 (hept, $J = 6.9$ Hz, 2H); 3.79 (s, 6H); 6.94 (d, $J = 8.4$ Hz, 2H); 7.16 (d, $J = 2.1$ Hz, 2H); 7.20 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.1$ Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 24.4; 33.5; 56.1; 111.2; 126.4; 128.0; 130.0; 140.7; 155.4. Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.50; H, 8.78; O, 10.72. Found: C, 80.44; H, 8.80.

4.2.7. 2,2′-Dihydroxy-5,5′-diisopropyldiphenyl 13. BBr_3 (2.1 g, 8.4 mmol) was added at 0 °C to a solution of **12** (1.32 g, 4.43 mmol) in CH_2Cl_2 (15 mL) and stirred at room temperature overnight. The excess of BBr_3 was decomposed by the dropwise addition of H_2O (15 mL) and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum to 10 mL. Crystals of **13** deposited on cooling. The precipitate was washed with hexane then dried under vacuum to give pure **13** (0.61 g, 2.26 mmol, 51%). ^1H NMR (300 MHz, $CDCl_3$, δ): 1.25 (d, $J = 6.6$ Hz, 6H); 2.90 (hept, $J = 6.9$ Hz, 2H); 5.60 (br s, 2H); 6.95 (d, $J = 8.4$ Hz, 2H); 7.12 (d, $J = 2.1$ Hz, 2H); 7.17 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.1$ Hz, 2H). ^{13}C NMR ($CDCl_3$, delta): 24.4; 33.5; 116.6; 123.8; 127.9; 129.2; 142.2; 151.0. Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20; O, 11.84. Found: C, 79.91; H, 8.23.

4.2.8. Preparation of the phosphites: representative procedure. A warm solution (60 °C) of biphenol (1 mmol) in dry toluene (25 mL) was slowly added to a solution of PCl_3 (1 mmol) and Et_3N (2 mmol), in dry toluene (5 mL). After 2 h of stirring, the reaction mixture was filtered under an argon atmosphere. The solution was dropwise added to a solution of DMAP (1 mmol) and Et_3N (8.2 mmol) in dry toluene (15 mL) at −60 °C over 2 h then **14** (1.1 mmol) was added, and the mixture allowed to warm to room temperature and stirred over 20 h. The solids were removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2–acetone, 97:3), affording the pure phosphite.

4.2.9. Methyl 3α-acetyloxy-12α-(5,5′-dibromobiphenyl-2,2′-diyl)phosphite-5β-cholan-24-oate 2. Yield 0.39 g (0.47 mmol, 41%). Mp = 63–65 °C; $[\alpha]_D^{22} = 24.3$ (c 1.00, CH_2Cl_2). ^1H NMR (300 MHz, benzene-d_6, δ): 0.44 (s, 3H); 0.67 (s, 3H); 0.98 (d, $J = 6.0$ Hz, 3H); 1–2.4 (m, 31H); 1.71 (s, 3H); 3.34 (s, 3H); 4.51 (m, 1H); 4.79 (m, 1H); 6.95 (d, $J = 8.4$ Hz, 1H); 7.00 (d, $J = 8.4$ Hz, 1H); 7.07 (d, $J = 2.4$ Hz, 1H); 7.08 (d, $J = 2.4$ Hz, 1H); 7.17–7.07 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.4$ Hz, 1H); 7.25 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.4$ Hz, 1H). ^{13}C NMR (50 MHz, benzene-d_6, δ): 12.2; 17.7; 17.8; 21.0; 22.9; 23.6; 26.0; 26.8; 27.0; 27.7; 28.7; 28.8; 31.0; 31.1; 32.4; 33.6; 34.2; 35.0; 35.8; 41.7; 46.6; 46.7; 47.8; 50.9; 73.8; 79.1 (d, $^2J = 17.1$ Hz); 118.1; 118.2; 123.9; 127.6; 128.2; 132.1 (d, $^3J = 2.6$ Hz); 132.2 (d, $^3J = 2.6$ Hz); 132.4; 132.7; 132.8; 148.9 (d, $^2J = 5.6$ Hz); 149.2 (d, $^2J = 6.1$ Hz); 169.5; 173.6. ^{31}P NMR (121 MHz, benzene-d_6, δ): 154.1. IR (KBr, cm^{-1}): 2961.9; 1732.8; 1472.0; 1393.4; 1261.0; 1190.7; 1110.8;

1027.5; 895.6; 799.1; 738.8; 714.0; 526.8. Anal. Calcd for $C_{39}H_{49}Br_2O_7P$: C, 57.08; H, 6.02; Br, 19.47; O, 13.65; P, 3.77. Found: C, 57.12; H, 6.00; Br, 19.45; P, 3.78.

4.2.10. Methyl 3α-acetyloxy-12α-(5,5′-diphenylbiphenyl-2,2′-diyl)phosphite-5β-cholan-24-oate 3. Yield 0.49 g (0.6 mmol, 68%). Mp = 71–73 °C; $[\alpha]_D^{24} = +28.6$ (*c* 0.95, CH_2Cl_2). ^{1}H NMR (300 MHz, benzene-d_6, δ): 0.50–2.09 (m, 37H); 0.5 (s, 3H); 0.72 (s, 3H); 1.12 (d, $J = 6.6$ Hz, 3H); 1.62 (s, 3H); 2.24–2.34 (m, 1H); 3.33 (s, 3H); 4.64–4.66 (m, 1H); 4.8–4.9 (m, 1H); 7.3–7.58 (m, 16H). ^{13}C NMR (75 MHz, benzene-d_6, δ): 12.3; 17.8; 17.9; 20.9; 23.0; 23.7; 26.0; 27.0; 27.2; 27.8; 28.9 (d, $^3J = 5.5$ Hz); 31.1; 31.2; 32.5; 33.6; 34.3; 35.2; 25.9; 36.0; 41.9; 46.5; 46.7 (d, $^3J = 4.0$ Hz); 47.7; 50.9; 74.0; 78.8 (d, $^2J = 17.5$ Hz); 122.8; 127.3; 127.4; 127.5; 128.8; 128.9; 129.2; 129.3; 132.1; 138.8; 138.9; 140.7; 149.6 (d, $^2J = 5.5$ Hz); 149.9 (d, $^2J = 6.0$ Hz); 169.6; 173.7. ^{31}P NMR (121 MHz, benzene-d_6, δ): 153.1. IR (KBr, cm^{-1}): 2962.3; 1735.6; 1601.4; 1478.2; 1448.3; 1363.2; 1261.3; 1192.9; 1097.6; 1020.7; 900.0; 859.4; 799.9; 760.2; 696.0; 644.2; 600.3; 561.4. Anal. Calcd for $C_{51}H_{59}O_7P$: C, 75.16; H, 7.30; O, 13.74; P, 3.80. Found: C, 75.20; H, 7.29; P, 3.82.

4.2.11. Methyl 3α-acetyloxy-12α-(5,5′-diisopropylbiphenyl-2,2′-diyl)phosphite-5β-cholan-24-oate 4. Yield 1.39 g (1.87 mmol, 76%). Mp = 55–60 °C; $[\alpha]_D^{25} = 52.0$ (*c* 1.03, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 0.74 .5 (s, 3H); 0.94–2.4 m, 31H); 0.94 (s, 3H); 1.03 (d, $J = 6.0$ Hz, 3H); 1.31 (d, $J = 3.9$ Hz, 3H); 1.32 (d, $J = 3.9$ Hz, 3H); 2.96–3.02 (m, 2H); 3.67 (s, 3H); 4.6–4.8 (m, 2H); 7.09–7.33 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 12.7; 17.8; 17.9; 21.7; 23.3; 23.9; 24.3; 24.4; 24.5; 26.3; 26.7; 27.3; 27.8; 28.7; 31.1; 31.4; 32.5; 33.8; 33.9; 34.0; 34.6; 35.3; 35.9; 36.1; 42.1; 46.5; 46.8; 46.9; 47.9; 51.7; 74.5; 78.4 (d, $^2J = 15.5$ Hz); 122.1; 122.2; 126.8; 126.9; 128.5; 129.3; 131.2 (d, $^3J = 3.1$ Hz); 131.4 (d, $^3J = 3.5$ Hz); 145.4; 145.6; 147.7 (d, $^2J = 5.6$ Hz); 148.2 (d, $^2J = 6$ Hz); 170.9; 174.9. ^{31}P NMR (121 MHz, benzene-d_6, δ): 154.3. IR (KBr, cm^{-1}): 2950.6; 2867.5; 1737.9; 1493.9; 1358.9; 1260.2; 1094.0; 1021.3; 927.9; 881.1; 798.0. Anal. Calcd for $C_{45}H_{63}O_7P$: C, 72.36; H, 8.50; O, 14.99; P, 4.15. Found: C, 72.41; H, 8.48; P, 4.16.

4.2.12. Enantioselective conjugate addition of diethylzinc to acyclic enones: general procedure. A solution of $Cu(OTf)_2$ (0.025 mmol) and phosphite (0.03 mmol) in freshly distilled solvent (5 mL) was stirred under a nitrogen atmosphere at rt for 1 h. The solution was cooled to the reaction temperature (see Tables 1–3) and diethylzinc (1.0 M in hexane, 1.5 mmol) was added. The enone was added slowly and stirring was continued at that temperature and the reaction was monitored by TLC. After complete conversion, the mixture was poured into 1 M HCl (25 mL) and extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated to yield the crude 1,4-products. The yields were determined by NMR analysis and the ees were determined by HPLC analyses.

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14. Toluene was used instead of ACN as this last has a freezing point too high for low temperature measurements and

toluene behaves as ACN with respect the M–P equilibrium position.[5]
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