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Application of deoxycholic acid-based copper–phosphite complexes as ligands in the enantioselective conjugate addition of diethylzinc to acyclic enones

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Abstract—Four phosphites obtained by linking enantiomerically pure binaphthylchlorophosphite to the two different hydroxy groups of deoxycholic acid were synthesized and used as chiral ligands in the enantioselective copper-catalyzed 1,4-addition of diethylzinc to acyclic enones. The ligands were screened for activity and enantioselectivity using chalcone as the substrate to establish the influence of the absolute configuration of the binaphthyl moiety as well as the position on the cholestanic backbone of the phosphite moiety. The ligand affording the best results was eventually used in the copper-catalyzed 1,4-addition to various acyclic enones, affording the alkylation products in good yields and e.e.s up to 78%.

1. Introduction

The requirement in modern organic synthesis for highly enantioselective C–C bond-forming reactions has directed scientists towards the development of chiral complexes that can efficiently promote the asymmetric conjugate addition of organozinc reagents to enones.[1] Good enantioselectivities have been realized in the copper-catalyzed Michael addition of diethylzinc to α,β-unsaturated carbonyl compounds using phosphoramidites,[2] amidophosphines,[3] phosphite–oxazolines,[4] diphosphites as chiral ligands.[5] More recently, the use of phosphites prepared starting from highly functionalized compounds with several stereogenic centers has emerged as an important tool for obtaining a series of chiral ligands that can be screened for high activity and enantioselectivity.[6]

Bile acids are very attractive compounds for such a purpose. In fact they possess a unique structure endowed with several stereogenic centers and hydroxy groups having different reactivity due to their different steric environment. Thanks to these features bile acids have been derivatized with different molecular units so that chiral auxiliaries having properties which depend on the nature of the moieties introduced have been obtained.[7] In addition, the use of arylcarbamoyl derivatives of bile acids as chiral selectors in enantioselective chromatography has demonstrated that the enantiodiscriminating properties of these compounds depend not only on the nature of the introduced moieties but also on the position where these units are located on the cholestanic backbone.[8]

On this basis, deoxycholic acid, **1**, possessing two hydroxy groups that can be reacted selectively, seems a good candidate for the preparation of enantiomerically pure phosphites. Since the two hydroxy groups have different reactivity, derivatives bearing the phosphite moiety at positions 3 and 12 of the cholestanic backbone can be obtained, which can exhibit different enantioselectivity depending on the position of the phosphite moiety. Herein we report the synthesis of four different deoxycholic based phosphites (Fig. 1) obtained by reacting suitable monohydroxy derivatives of deoxycholic acid with (*R*)- and (*S*)-binaphthyl chlorophosphites and their screening for activity and enantioselectivity in the copper-catalyzed enantioselective conjugate addition of diethylzinc to acyclic enones.

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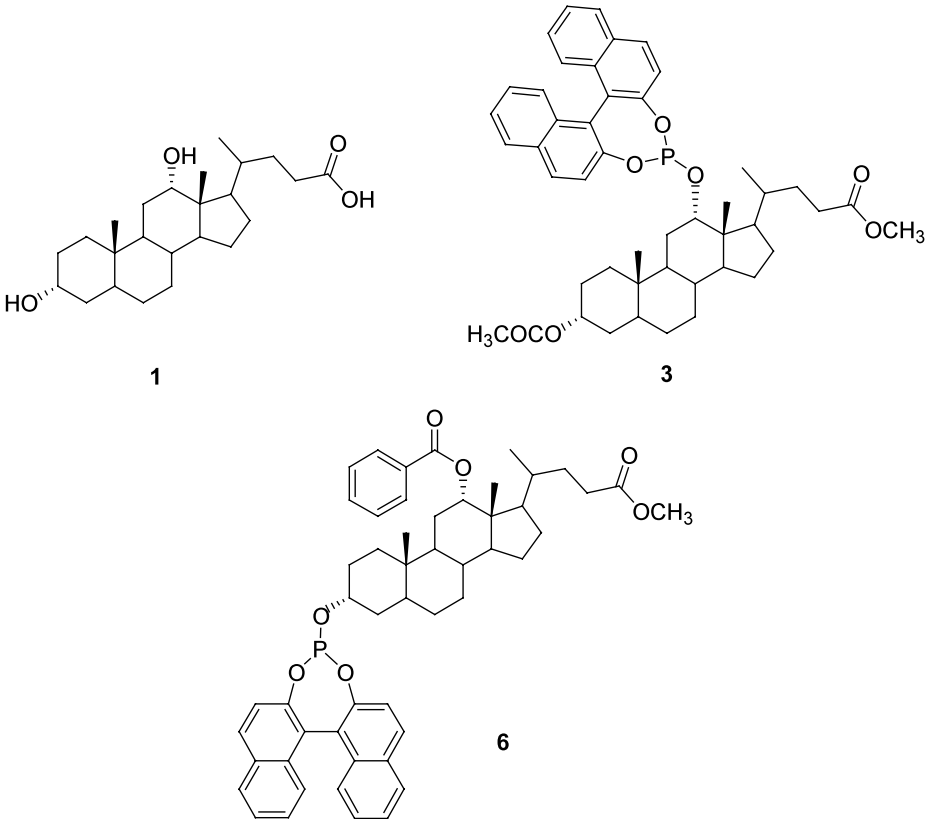


Figure 1. Structures of deoxycholic acid and phosphite derivatives.

2. Results and discussion

2.1. Synthesis of phosphites

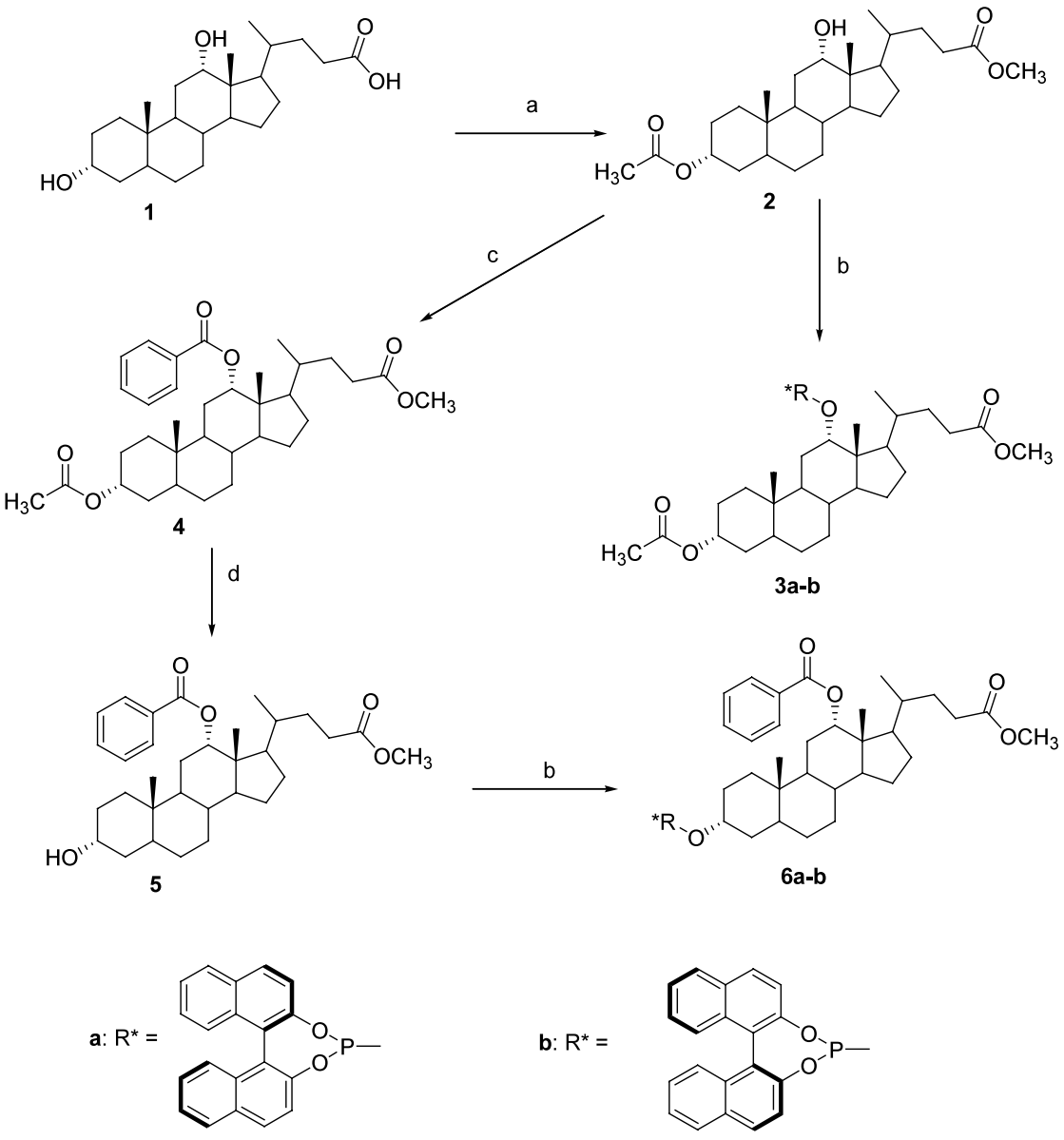
The synthesis of the four cholic acid-based phosphites is summarized in Scheme 1. In order to obtain the derivative bearing the binaphthylphosphite moiety at position 12 of the cholestanic backbone, protection of the 3-OH group is required. Of course, transformation of the free carboxyl group into the corresponding methyl ester before derivatization of the 12-OH group is also mandatory. Protection of the two functional groups was obtained in one step, by reacting deoxycholic acid with methyl acetate[9] in the presence of *p*-toluenesulphonic acid and water, which afforded the corresponding 3-acetoxy methylcholate **2** in very good yield. Under these experimental conditions the axial 12-OH group does not react at all. The treatment of **2** with (*S*)- and (*R*)-binaphthyl chlorophosphite, prepared starting from binaphthol and PCl_3 according to standard procedures,[2b] in the presence of triethylamine and DMAP afforded, after chromatographic purification, the enantiomerically pure phosphites **3** in 60% yield.

In order to obtain a deoxycholic acid derivative bearing the phosphite moiety at the 3 position of the cholestanic backbone, we needed a methylcholate derivative with the 12-OH group protected. Since the 3-OH moiety is more reactive than the 12-OH group, direct protection of the 12-OH group was unrealizable. To obtain such a derivative it is necessary to initially protect the more reactive 3-OH group and afterwards the 12-OH: of course, the 3-OH protecting group must be cleaved selectively over the 12-OH protecting group. This strategy can be accomplished by protecting the 3-OH as the acetate ester and subsequently protecting the 12-OH as the benzoate ester, which is stable under the mild acidic conditions used to cleave the 3-acetate group.

As reported in Scheme 1, compound **2** was reacted with CaH_2 in the presence of benzyltriethylammonium chloride as phase transfer catalyst followed by addition of benzoyl chloride, affording derivative **4** in excellent yield after chromatographic purification. The reaction of **4** with HCl in methanol gave derivative **5** in quantitative yield, which was reacted with (*R*)- and (*S*)-binaphthyl chlorophosphites affording the phosphites **6** in 60% yield after chromatographic purification.

2.2. Conjugate addition to acyclic enones

Chiral auxiliaries **3** and **6** were assayed in the copper-catalyzed conjugate addition of diethylzinc to acyclic enones. In a typical procedure the catalytic system was generated in situ by stirring a solution containing the ligand and the copper salt for 1 h at room temperature, followed by addition of diethylzinc. The effect of different reaction parameters was investigated using ligand **3a** and chalcone as a substrate and the obtained results are summarized in Table 1.



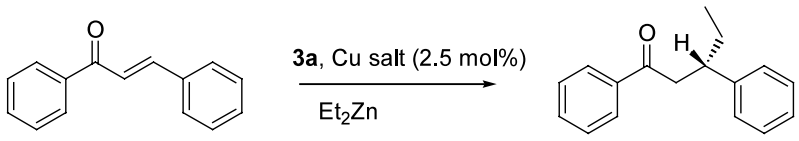
Scheme 1. *Reagents and conditions*: (a) methyl acetate, TsOH, H_2O, reflux, 24 h; (b) triethylamine, DMAP, binaphthylchlorophosphite, THF, −60 to rt, 20 h; (c) CaH_2, benzyltriethylammonium chloride, benzoyl chloride, toluene, reflux, 24 h; (d) HCl, methanol, rt, 20 h.

All the reactions were stopped when conversion of the substrate was complete or did not proceed further, as judged by TLC analysis. The conjugate addition of diethylzinc in the presence of the catalytic species obtained from **3a** and $Cu(OTf)_2$ in molar ratio 1.2:1 at −20°C affords the alkylated product in 87% yield and 59% e.e. after 2 h (entry 1). Increasing the ligand/Cu salt ratio did not affect the outcome of the reaction: in fact, the alkylation product was obtained in comparable yield and e.e (entry 2). On lowering the temperature an improvement in the enantioselectivity was achieved without loss of catalytic activity (entry 3). Worse results in terms of both activity and enantioselectivity were obtained on moving from toluene to dichloromethane as the solvent (entry 4). Varying the copper salt showed that the use of $Cu(OTf)_2$ seems to be mandatory: its replacement with CuOTf gave poorer results both in terms of yield and enantioselectivity (entry 5). The results were even worse using CuI (entry 6): the catalytic activity of the system dropped dramatically and the alkylation product was obtained in only 46% yield after 24 h. The use of CuI was also detrimental to the enantioselectivity of the process, the alkylation product being obtained with 6% e.e.

On the basis of these results, for comparative purposes, the other ligands were assayed under the experimental conditions which afforded the best results, i.e. ligand to copper ratio of 1:1.2, $Cu(OTf)_2$ as copper salt, temperature of −70°C and toluene as solvent. The results are listed in Table 2.

Perusal of Table 2 shows that all the deoxycholic acid-based ligands form catalytic species, which were

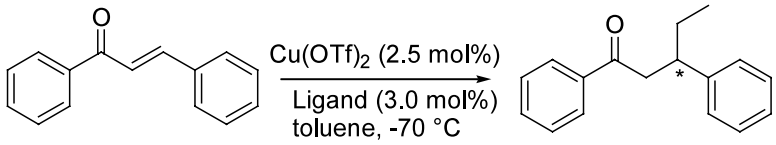
Table 1. Catalytic enantioselective conjugate addition to chalcone in the presence of **3a**



Entry	Cu salt	**3a** (mol%)	Time (h)	Solvent	Temp. (°C)	Yield (%)[a]	E.e. (%)[b]	A.C.[c]
1	$Cu(OTf)_2$	3.0	2	Toluene	−20	87	59	*S*
2	$Cu(OTf)_2$	6.0	2	Toluene	−20	81	58	*S*
3	$Cu(OTf)_2$	3.0	3	Toluene	−70	86	76	*S*
4	$Cu(OTf)_2$	3.0	7	CH_2Cl_2	−70	58	60	*S*
5	CuOTf	3.0	3.5	Toluene	−70	58	60	*S*
6	CuI	3.0	24	Toluene	−70	46	6	*S*

[a] Isolated yield.
[b] Determined by HPLC analyses on Chiralcel OJ, 254 nm, 1.0 ml/min, hexane:2-propanol, 99.5:0.5.
[c] Determined by the sign of the specific rotation.

Table 2. Catalytic enantioselective conjugated addition to chalcone

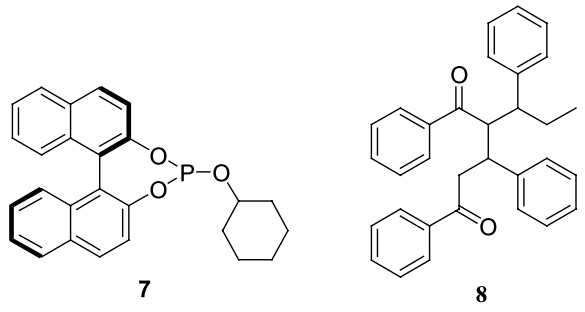


Entry	Ligand	Time (h)	Yield (%)[a]	E.e. (%)[b]	A.C.[c]
1	**3a**	3	86	76	*S*
2	**3b**	3	88	40	*R*
3	**6a**	3	88	58	*S*
4	**6b**	3	85	6	*R*
5	**7**	20	46	32	*S*
6	**7**[d]	20	54	34	*S*

[a] Isolated yield.
[b] Determined by HPLC analyses on Chiralcel OJ, 254 nm, 1.0 ml/min, hexane:2-propanol, 99.5:0.5.
[c] Determined by the sign of the specific rotation.
[d] Performed with 6 mol% of ligand.

very reactive in the conjugate addition of diethylzinc to chalcone, affording the alkylation product in good yield after 3 h (entries 1–4). The comparable yields indicate that the catalytic activity of the formed species is independent of the structure and stereochemistry of the starting ligand. On the contrary, both the structure and stereochemistry of the ligands strongly affect the enantioselectivity of the reaction. As far as the absolute configuration of the stereogenic binaphthyl moiety is concerned, ligand **3a**, which contains an *R*-configurated binaphthylic moiety afforded the alkylation product with 76% e.e., whereas its diastereoisomer **3b** gave 1,3-diphenylpentan-1-one with 40% e.e.

The effect of the structure of the ligand on the enantioselectivity can be established by comparing the results obtained using ligands **3a** and **6a** (entries 1 and 3), which have a *R* configurated binaphthylphosphite moiety linked at the two different hydroxy-substituted positions of the cholestanic backbone. The higher e.e. obtained using **3a**, suggests that linking the binaphthylphosphite moiety to the more sterically demanding 12-position gives rise to a more enantioselective ligand. Additionally, in the case of ligands **6a**–**b** the matched couple is still that possessing the (*R*)-binaphthyl moiety: when **6b**, which has an (*S*)-binaphthyl moiety, was used as the chiral ligand the alkylation product was obtained with only 6% e.e. This result also indicates that the difference between the e.e. obtained using the matched or mismatched couple is strongly dependent on the position of the binaphthylphosphite moiety on the cholestanic backbone. The difference in e.e. is 76 versus 40% when the binaphthylphosphite moiety is linked at the 12-position of the deoxycholic acid, whereas it is 58 versus 6% when the binaphthylphosphite moiety is linked at the 3-position. However, the deoxycholic moiety does not exert its influence on the sense of the asymmetric induction and an (*S*)-configurated product is always obtained when using ligands possessing an (*R*)-binaphthyl moiety, as observed with other phosphorous ligands.[2b,4b] In order to evaluate the influence of the binaphthol moiety on the enantioselectivity we tested (*R*)-(1,1′-binaphthyl-2,2′-diyl) cyclohexyl phosphite **7**, which is chiral only by virtue of the



7 8

Figure 2. Structure of (*R*)-(1,1′-binaphthyl-2,2′-diyl)cyclohexyl phosphite **7** and side-product **8**.

binaphthol moiety. This ligand shows lower activity and enantioselectivity with respect to the deoxycholic ligands. Under the experimental conditions used with the other ligands the conversion of the substrate was complete after 20 h, as judged by TLC, and the isolated yield was only 46%. The lower yield is due to the formation of the side-product **8**, generated by attack of the enolate formed in situ on another molecule of unreacted substrate, as already observed with other ligands.[10] Side product **8** was isolated and characterized by NMR.

Both the yield and e.e. did not improve significantly even after increasing the ligand to copper ratio (entry 6). The obtained e.e. suggests that the chirality of the binaphthol alone is sufficient to induce enantioselectivity, but the asymmetric induction is helped by the presence of the deoxycholic acid moiety when it is in a matched relationship with the binaphthyl moiety. In addition, the deoxycholic acid moiety deeply affects the activity of the formed catalytic species: Using **7** longer reaction time is required to observe complete conversion of the substrate and the product is obtained in lower yield (Fig. 2).

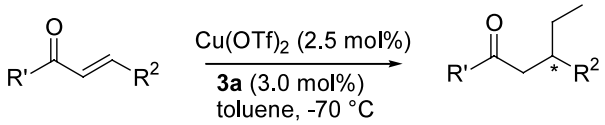
Screening of the deoxycholic based ligands **3a**–**b** and **6a**–**b** has shown that phosphite **3a** is the best ligand to promote the enantioselective conjugate addition of diethylzinc to chalcone. In order to evaluate the influence of the substrate structure on the activity and enantioselectivity of the catalytic species formed from **3a**, screening of differently substituted acyclic enones was performed and the results are reported in Table 3.

The presence of an arylketone moiety, as already observed with phosphoramidite ligands,[2a] seems to be important for a satisfactory degree of asymmetric induction: in passing from chalcone to benzylideneacetone (entry 2) the enantioselectivity dropped to 40%. The effect of electronic factors on the outcome of the reaction can be investigated using *para*-substituted chalcones. The presence of an electron-donating group effects a slight lowering of asymmetric induction (entry 3), whereas a chlorine substituent does not significantly affect the enantioselectivity of the process. On the contrary, differences in the activity of the catalytic species depending on the substrate structure were not observed and comparable yields were obtained with the four different substrates (entries 1–4). Different considerations have to be made when the chalcone possesses a strong electron-withdrawing substituent, such as the CF_3 group (entry 5). In this case both activity and enantioselectivity of the catalytic system fell dramatically and the alkylation product was obtained in 22% yield and 16% e.e. after 20 h. The very low yield was due to partial conversion of the substrate and the formation of by-products. Again, formation of the dimeric compound generated by conjugate addition of the in situ formed zinc enolate to the unreacted substrate was observed, suggesting that this reaction becomes competitive when the 1,4 addition of diethylzinc is slow.

3. Conclusions

Four phosphite ligands, derived from inexpensive deoxycholic acid, were screened in the enantioselective conjugate addition of diethylzinc to chalcone. Changing the absolute configuration at the stereogenic binaphthyl

Table 3. Catalytic enantioselective conjugate addition to acyclic enones



Entry	R^1	R^2	Time (h)	Yield (%)[a]	E.e. (%)
1	Ph	Ph	3	82	76[b]
2	Me	Ph	3	80	40[c]
3	Ph	*p*-OMe(C_6H_4)	3	78	60[d]
4	Ph	*p*-Cl(C_6H_4)	3	84	78[b]
5	Ph	*p*-CF_3(C_6H_4)	20	22	16[e]

[a] Isolated yield.
[b] Determined by HPLC analyses on Chiralcel OJ, 254 nm, 1.0 ml/min, hexane:2-propanol, 99.5:0.5.
[c] Chiralcel OJ, 254 nm, 0.5 ml/min, hexane:2-propanol, 99.5:0.5.
[d] Chiralcel OJ, 254 nm; 1.0 ml/min, hexane:2-propanol, 99:1.
[e] Chiralcel OJ, 254 nm, 1.0 ml/min, hexane.

moiety has allowed us to find the matched couples of the ligands. The nature of the deoxycholic moiety, possessing two hydroxy groups having different reactivity due to their different steric environment has allowed us to vary the position of binaphthylphosphite moiety on the steroidal skeleton and hence to find the best substitution pattern for high levels of activity and enantioselectivity. In fact, although the binaphthyl moiety governs the sense of asymmetric induction and the matched couple is always that possessing an (*R*)-binaphthylphosphite, the position of the phosphite moiety on the cholestanic backbone has a strong influence on the enantioselectivity of the reaction. The best combination of position on the cholestanic backbone–binaphthol absolute configuration was found and ligand **3a** has emerged as the most suitable to obtain high yields as well as good asymmetric induction. Thus, **3a** was used in the catalytic conjugate addition of diethylzinc to structurally different acyclic enones, affording high yields and satisfactory enantioselectivities in most of the cases examined.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Gemini-200 200 MHz NMR spectrometer, using TMS as external standard. ^{31}P NMR spectra were recorded in benzene-D_6: ppm are referred to H_3PO_4 as external standard. The following abbreviation are used: s = singlet, d = doublet, dd = double doublet, t = triplet, m = multiplet, br = broad. TLC analyses were performed on silica gel 60 Macherey–Nagel sheets; flash chromatography separations were carried out on adequate dimension columns using silica gel 60 (230–400 mesh). HPLC analyses were performed on a JASCO PU-980 intelligent HPLC pump equipped with a JASCO UV-975 detector. Optical rotations were measured with a JASCO DIP-360 digital polarimeter. Melting points were obtained using a Kofler Reichert–Jung apparatus and are uncorrected. The IR spectra were recorded on a Perkin–Elmer 1710 spectrofotometer. Toluene and THF were heated under reflux over sodium–benzophenone and distilled before the use. Unless otherwise specified the reagents were used without any purification. Methyl 3α-acetyloxy-12α-hydroxy-5β-cholan-24-oate[9] **2**, (*R*)- and (*S*)-binaphthyl chlorophosphite[2a] and the substituted unsaturated ketones[11] were obtained according to literature procedures.

4.2. Methyl 3α-acetyloxy-12α-benzoyloxy-5β-cholan-24-oate, 4

CaH_2 (0.15 g), $Et_3BnN^+Cl^-$ (0.08 g) and benzoyl chloride (0.3 ml) were added to a solution of **2** (1 g, 2.15 mmol) in dry toluene (15 ml) and the mixture was heated under reflux for 24 h. The reaction mixture was cooled to rt then water and CH_2Cl_2 were added. The organic layer was separated and the aqueous phase was extracted twice with CH_2Cl_2. The organic extracts were treated with a 10% solution of HCl, a 5% solution of $NaHCO_3$ and water in that order, then dried over anhydrous Na_2SO_4. Evaporation of the solvent under vacuum afforded the crude product, which was purified by flash chromatography (CH_2Cl_2:acetone, 97:3) giving pure **3** (1 g, 1.75 mmol, 82%). Mp 48–50°C; $[\alpha]_D^{20}$ 65.9 (*c* 0.9; CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$, δ): 8.03 (d, 2H, aromatics), 7.55 (m, 3H, aromatics), 5.31 (s, 1H, 12CH), 3.59 (s, 3H, $OC\underline{H}_3$), 4.61 (m, 1H, 3CH), 1.91 (s, 3H, $C\underline{H}_3CO$) 2.27–0.97 (m, 23H, steroidal CH and CH_2), 0.91 (s, 3H, CH_3), 0.81 (s, 3H, CH_3), 0.82 (d, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$, δ): 12.8, 17.7, 21.6, 23.3, 23.8, 26.1, 26.3, 26.6, 27.1, 27.6, 31.1, 31.2, 32.5, 34.3, 34.9, 35.0, 36.0, 42.0, 45.8, 48.2, 50.3, 51.7, 74.3, 76.8, 128.7, 129.7, 131.1, 133.1, 166.1, 170.8, 174.8.

4.3. Methyl 3α-hydroxy-12α-benzoyloxy-5β-cholan-24-oate, 5

Concentrated HCl (1.07 ml) was added to a solution of **2** (1g, 1.75 mmol) in CH_3OH (43 ml). The reaction mixture was stirred overnight at rt, then poured into water. The mixture was extracted with CH_2Cl_2, and the organic phase was treated with a 10% solution of HCl, a 5% solution of $NaHCO_3$ and water in that order, then dried over anhydrous Na_2SO_4. After removing the solvent at reduced pressure, pure **5** was obtained in quantitative yield. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 8.03 (d, 2H, aromatics), 7.50 (m, 3H, aromatics), 5.31 (s, 1H, 12CH), 3.59 (s, 3H, $OC\underline{H}_3$), 3.51 (m, 1H, 3CH), 2.32–0.85 (m, 23H, steroidal CH and CH_2), 0.91 (s, 3H, CH_3), 0.81 (s, 3H, CH_3), 0.82 (d, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$, δ): 12.8, 17.7, 23.4, 23.8, 26.0, 26.4, 27.3, 27.6, 30.7, 30.8, 31.1, 31.2, 34.3, 34.9, 35.3, 36.1, 36.6, 42.2, 45.8, 48.2, 50.2, 51.7, 71.9, 76.8, 128.8, 129.7, 131.0, 133.2, 166.2, 174.8.

4.4. Preparation of the phosphites: representative procedure

A solution of freshly prepared binaphthyl chlorophosphite (3 mmol) in dry toluene (30 ml) was added dropwise to a solution of DMAP (3.27 mmol) and Et_3N (31 mmol) in dry toluene (50 ml) at −60°C over 2 h. The deoxycholic acid derivative (or cyclohexanol) was then added and the mixture was allowed to warm to rt and stirred for 20 h. After removing the solvent at reduced pressure the crude product was purified by column chromatography (SiO_2, CH_2Cl_2–aceton, 95–5), affording the pure phosphites as white foamy solids.

4.4.1. Methyl 3α-acetoxy-12α [(*R*)-(1,1′-binaphthyl-2,2′-diyl)phosphite]-5β-cholan-24-oate, 3a. Yield 1.4 g (1.83 mmol, 61%). Mp 100–102°C; $[\alpha]_D^{25}$ −159.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6, δ): 0.47 (s, 3H, CH_3), 0.69 (s, 3H, CH_3), 1.09 (d, *J* 6.6 Hz, 3H, CH_3), 1.60 (s, 3H, CH_3CO), 0.51–2.42 (m, 25H, steroidal CH and CH_2), 3.41 (s, 3H, OCH_3), 4.58 (dd, J_1 2 Hz, J_2 5.5 Hz, 1H, H_{12}), 4.79 (m, *J* 5 Hz, 1H, H_3), 6.83 (m, 2H, aromatics), 7.00 (m, 2H, aromatics), 7.08 (m, 2H, aromatics), 7.34 (d, *J* 8.5 Hz, 1H, aromatic), 7.41 (d, *J* 8.5 Hz, 1H, aromatic), 7.59 (m, 2H, aromatics), 7.67 (d, *J* 8.5 Hz, 1H, aromatic), 7.81 (d, *J* 8.5 Hz, 1H, aromatic);

^{13}C NMR (75 MHz, C_6D_6, δ): 12.8, 18.1, 21.4, 23.4, 24.1, 26.1, 27.3, 27.5, 28.3, 29.4 (d, J_{C-P} 7.5 Hz), 31.8, 31.9, 32.9, 33.7, 34.7, 35.8, 35.9, 36.3, 36.7, 42.3, 47.1 (d, J_{C-P} 6 Hz), 47.4, 48.1, 51.4, 74.5, 79.4 (d, J_{C-P} 16.6 Hz), 122.5, 123.0, 125.3, 126.7, 127.1, 127.7, 127.9, 128.9 (d, J_{C-P} 4.5 Hz), 130.3, 130.9, 131.9, 132.3, 133.7, 133.9, 148.9, 149.2 (d, J_{C-P} 6 Hz), 170.1, 174.2; ^{31}P NMR (121 MHz, C_6D_6, δ): 155.9.

4.4.2. Methyl 3α-acetoxy-12α [(*S*)-(1,1′-binaphthyl-2,2′-diyl)phosphite]-5β-cholan-24-oate, 3b. Yield 1.4 g (1.83 mmol, 61%). Mp 128–130°C. $[\alpha]_D^{25}$ 240.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6, δ): 0.54 (s, 3H, CH_3), 0.76 (s, 3H, CH_3), 1.16 (d, *J* 9 Hz, 3H, CH_3), 1.68 (s, 3H, CH_3CO), 0.57–2.51 (m, 25H, steroidal CH and CH_2), 3.48 (s, 3H, OCH_3), 4.65 (dd, J_1 3 Hz, J_2 6 Hz, 1H, H_{12}), 4.87 (m, *J* 6 Hz, 1H, H_3), 6.90 (m, 2H, aromatics), 7.06 (dd, *J* 6 Hz, 2H, aromatics), 7.14 (m, 2H, aromatics), 7.41 (d, *J* 9 Hz, 1H, aromatic), 7.49 (d, *J* 9 Hz, 1H, aromatic), 7.71 (m, 2H, aromatics), 7.75 (d, *J* 9 Hz, 1H, aromatic), 7.89 (d, *J* 9 Hz, 1H, aromatic); ^{13}C NMR (75 MHz, C_6D_6, δ): 12.4, 17.7, 21.0, 23.0, 23.7, 25.8, 26.9, 27.2, 27.9, 29.1 (d, J_{C-P} 8 Hz), 31.4, 31.5, 32.5, 33.4, 34.3, 35.3, 35.9, 36.3, 41.9, 46,7(d, J_{C-P} 4.5 Hz), 47.0, 47.7, 51.0, 74.1, 79.0 (d, J_{C-P} 17.2 Hz), 122.1, 122.6, 124.9, 125.1, 126.3, 126.5, 127.3, 128.5 (d, J_{C-P} 3.5 Hz), 129.8, 130.5, 131.6, 131.9, 133.3, 133.5, 148.5 (d, J_{C-P} 3 Hz), 148.8 (d, J_{C-P} 5.5 Hz), 169.6, 173.8; ^{31}P NMR (121 MHz, C_6D_6, δ): 155.2.

4.4.3. Methyl 3α [(*R*)-(1,1′-binaphthyl-2,2′-diyl)-phosphite]-12α-benzoyloxy-5β-cholan-24-oate, 6a. Yield 1.5 g (1.95 mmol, 60%). Mp 110–112; $[\alpha]_D^{25}$ −172 (*c* 0.7, CH_2Cl_2); ^{1}H NMR (300 MHz, C_6D_6, δ): 0.59 (s, 3H, CH_3), 065 (s, 3H, CH_3) 0.90 (d, *J* 6 Hz, 3H, CH_3), 0.44–2.22 (m, 25H, steroidal CH and CH_2), 3.36 (s, 3H, OCH_3), 4.12 (m, *J* 6 Hz, 1H, H_3), 5.56 (br s, 1H, H_{12}), 6.74–7.26 (m, 8H, aromatics), 7.33 (d, *J* 8.7 Hz, 1H, aromatic), 7.48 (m, 3H, aromatics), 7.64 (m, 3H, aromatics) 8.30 (dd, J_1 2.1 Hz, J_2 8.4 Hz, 2H, aromatics), ^{13}C NMR (75 MHz, C_6D_6, δ): 12.6, 17.7, 22.8, 23.8, 26.2, 26.3, 26.8, 27.6, 29.8, 31.0, 33.8, 34.9, 35.0, 35.5, 35.9, 42.0, 45.8, 48.3, 50.4, 50.9, 76.2, 78.0, 122.2, 123.8, 125.1, 125.6,126.6, 128.3, 128.8, 129.6, 129.8, 131.4 (d, J_{C-P} 4.2 Hz), 131.9, 133.1, 133.2, 133.4,148.4, 149.2 (d, J_{C-P} 4.9 Hz), 165.8, 173.6; ^{31}P NMR (121 MHz, C_6D_6, δ): 147.3.

4.4.4. Methyl 3α [(*S*)-(1,1′-binaphthyl-2,2′-diyl)-phosphite]-12α-benzoyloxy-5β-cholan-24-oate, 6b. yield 1.6 g (1.95 mmol, 65%). Mp 98–100°C; $[\alpha]_D^{25}$ 264 (*c* 1.15, CH_2Cl_2); ^{1}H NMR (300 MHz, C_6D_6, δ): 0.52 (s, 6H, CH_3), 0.83 (d, *J* 6.3 Hz, 3H, CH_3), 0.38–2.07 (m, 25H, steroidal CH and CH_2), 3.72 (s, 3H, OCH_3), 3.97 (m, *J* 6 Hz, 1H, H_3), 5.49 (br s, 1H, H_{12}), 6.84–7.10 (m, 7H, aromatics), 7.37 (m, *J* 8.7 Hz, 4H, aromatics), 7.56 (m, 4H, aromatics), 8.20 (dd, J_1 2.1 Hz, J_2 8.4 Hz, 2H, aromatics); ^{13}C NMR (75 MHz, C_6D_6, δ): 12.7, 17.7, 22.8, 23.7, 26.2, 26.3, 26.9, 27.6, 29.4, 31.0, 33.7, 34.9, 35.0, 35.6, 35.8, 41.7, 45.7, 48.2, 50.6, 50.9, 76.1, 76.3, 122.2, 123.3, 125.0, 125.6,126.6, 128.8, 129.3, 129.5, 129.9, 131.4 (d, J_{C-P} 4.2 Hz), 131.9, 133.0, 133.2, 133.4,148.4, 149.5 (d, J_{C-P} 5.5 Hz), 165.8, 173.6; ^{31}P NMR (121 MHz, C_6D_6, δ): 142.6.

4.4.5. (*R*)-(1,1′-binaphthyl-2,2′-diyl) cyclohexyl phosphite, 7. 0.74 g (1.8 mmol, 60% yield). Mp 78–80°C (dec.); $[\alpha]_D^{25}$ −303 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6, δ): 0.93 (m, 4H, cyclohexyl), 1.47 (m, 4H, cyclohexyl), 1.75 (br s, 2H, cyclohexyl), 4.13 (br s, 1H, CH), 6.89 (q, *J* 8 Hz, 2H, aromatics), 7.10 (q, *J* 7.5 Hz, 2H, aromatics), 7.42 (d, *J* 8.5 Hz, 2H, aromatics), 7.46 (d, *J* 9 Hz, 2H, aromatics), 7.54 (d, *J* 9 Hz, 1H, aromatic), 7.58 (d, *J* 8 Hz, 1H, aromatic), 7.61 (d, *J* 8.5 Hz, 2H aromatics); ^{13}C NMR (75 MHz, C_6D_6, δ): 23.5, 25.2, 34.3, 34.6, 74.5, 122.1, 122.2, 123.3, 124.9 125.0, 126.4, 126.5, 128.1, 128.2, 128.4, 128.6, 129.8, 130.7, 131.3, 131.9, 133.2, 133.4, 148.3, 149.3.

4.5. 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 toluene (5 ml) was stirred under nitrogen atmosphere at rt for 1 h. The solution was cooled to −70°C and diethylzinc (1.0 M in hexane, 1.5 mmol) was added. The enone was added slowly and stirring was continued at −70°C and the reaction was monitored by TLC. After complete conversion the mixture was poured in 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. After purification by column chromatography (SiO_2 and hexane/diethyl ether 80/20), the e.e.s were determined by HPLC analyses.

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References

1. (a) Krause, N.; Hoffmann-Roder, A. *Synthesis* **2001**, 171–196; (b) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221–3236.
2. (a) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346–353; (b) Arnold, L. A.; Imbos, R.; Mandoli, A.; de Vries, A. H. M.; Nassz, R.; Feringa, B. L. *Tetrahedron* **2000**, *56*, 2865–2878; (c) de Vries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem., Int. Ed.* **1996**, *35*, 2374–2376; (d) Zhang, F. Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1998**, *9*, 1179–1182; (e) Huttenloch, O.; Spieler, J.; Waldmann, H. *Chem. Eur. J.* **2001**, *7*, 671–675; (f) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262–5263; (g) Alexakis, A.; Rosset, S.; Allamand, J.; March, S.; Guillen, F.; Benhaim, C. *Synlett* **2001**, 1375–1378.
3. Hu, X.; Chen, H.; Zhang, X. *Angew. Chem., Int. Ed.* **1999**, *38*, 3518–3521.
4. (a) Knobel, A. K. H.; Escher, I. H.; Pfaltz, A. *Synlett* **1997**, 1429–1431; (b) Escher, I. H.; Pfaltz, A. *Tetrahedron* **2000**, *56*, 2879–2888.

5. (a) Pamies, O.; Dieguez, M.; Net, G.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2000**, *11*, 4377–4383; (b) Alexakis, A.; Burton, J.; Vastra, J.; Benhaim, C.; Fournioux, X.; van den Heuvel, A.; Leveque, J. M.; Mazé, F.; Rosset, S. *Eur. J. Org. Chem.* **2000**, 4011–4027; (c) Liang, L.; Au-Yeung, T. L.; Chan, A. S. C. *Org. Lett.* **2002**, *4*, 3799–3801.
6. (a) Dieguez, M.; Net, G.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2001**, *12*, 2895–2900; (b) Alexakis, A.; Benhaim, C.; Fournioux, X.; van den Heuvel, A.; Leveque, J. M.; March, S.; Rosset, S. *Synlett* **1999**, 1811–1813.
7. (a) D'Souza, L.; Maitra, U. *J. Org. Chem.* **1996**, *61*, 9494–9502; (b) Potluri, V. K.; Maitra, U. *J. Org. Chem.* **2000**, *65*, 7764–7769; (c) Ono, Y.; Nakashima, K.; Sano, M.; Kanekiyo, Y.; Inoue, K.; Hojo, J.; Shinkai, S. *Chem. Commun.* **1998**, 1477–1478; (d) Gdaniec, M.; Milewska, M. J.; Polonski, T. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 392–395; (e) Bartolini, O.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Chem. Commun.* **2000**, 365–366; (f) Maitra, U.; Mathivanan, P. *Tetrahedron: Asymmetry* **1994**, *5*, 1171–1174; (g) Maitra, U.; Bag, B. G. *J. Org. Chem.* **1992**, *57*, 6979–6981; (h) Maitra, U.; Mathivanan, P. *J. Chem. Soc., Chem. Commun.* **1993**, 1469–1471; (i) Bandyopadhyaya, A. K.; Sangeetha, N. M.; Maitra, U. *J. Org. Chem.* **2000**, *65*, 8239–8244.
8. (a) Iuliano, A.; Salvadori, P.; Félix, G. *Tetrahedron: Asymmetry* **1999**, *10*, 3353–3364; (b) Iuliano, A.; Masini, G.; Salvadori, P.; Félix, G. *Tetrahedron: Asymmetry* **2001**, *12*, 2811–2825; (c) Iuliano, A.; Pieraccini, I.; Salvadori, P.; Félix, G. *Tetrahedron: Asymmetry* **2002**, *13*, 1265–1275.
9. Kuhaida, K.; Kandrac, J.; Cirin-Novta, V.; Milkovic, D. *Collect. Czech. Chem. Commun.* **1996**, *61*, 1073–1076.
10. Delapierre, G.; Constantieux, T.; Brunel, J. M.; Buono, G. *Eur. J. Org. Chem.* **2000**, 2507–2511.
11. Hassner, A.; Cromwell, N. H. *J. Am. Chem. Soc.* **1958**, *80*, 893–900.