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Stereochemical Features Making Deoxycholic Acid Derived *tropos* Biphenylphosphites Efficient Chiral Ligands for Rhodium: The Asymmetric Hydrogenation of Dimethylitaconate as a Case Study

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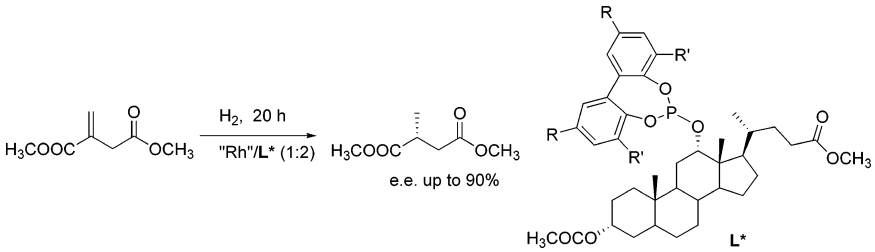

Different deoxycholic acid derived biphenylphosphites, whose *tropos* nature was ascertained by NMR and CD measurements, were used in the rhodium-catalyzed asymmetric hydrogenation of dimethylitaconate achieving enantiomeric excesses up to 91%. The comparison of these results to those obtained using the corresponding atropoisomeric binaphthyl analogues, together with NMR and CD measurements on the rhodium complexes of some phosphites, allowed us to shed light on the nature of the active catalytic species and on the asymmetric induction process and hence to recognize the most appropriate stereochemical features to reach good levels of enantioselectivity.

Introduction

The rhodium-catalyzed asymmetric hydrogenation of functionalized olefins represents one of the most extensively used enantioselective reactions not only at the academic level but also for the industrial preparation of enantiomerically enriched pharmaceutical compounds.[1] High levels of asymmetric induction were reached using chiral bidentate phosphine ligands[2] and, for about 30 years, the formation of a conformationally defined metallocycle, guaranteed by the use of a C_2 bisphosphorous ligand,[3] was considered mandatory for the stereochemical outcome of the reaction. This prompted scientists to dedicate several efforts to the preparation of new and more efficient chiral ligands having these structural features.[2] However, synthesis of these kinds of ligands is often cumbersome, time-consuming, and expensive; therefore, the breakthrough of Feringa,[4] Pringle,[5] and Reetz[6] that monodentate phosphorus ligands can successfully promote the asymmetric catalytic hydrogenation with high level of enantioselectivity represented a turning point in the design of efficient chiral auxiliaries for this reaction. In fact, monophosphorous ligands, such as phosphites, phosphoramidites, and phosphinites having different structures[7] show the advantage of being easily accessible and quite inexpensive and, in addition, of possessing comparable or even better enantioselectivity than bidentate phosphorus ligands.[8] Thus, the last 5 years have witnessed an explosive growth of newly designed monophosphorous ligands to be used in the rhodium-catalyzed asymmetric hydrogenation.[9] Further progress in the design of inexpensive and readily accessible ligands is represented by the asymmetric activation of *tropos* species[10] in the synthesis of

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phosphites and phosphoramidites, a synthetic strategy which avoids the sometimes difficult and time-consuming resolution step. According to this strategy, a configurationally fluxional (*tropos*) phosphorus ligand can be obtained starting from an achiral biphenol and a configurationally stable amine or alcohol, which induces a prevalent sense of twist on the biphenyl moiety in the formation of the phosphite or phosphoramidite species or when the phosphorus ligand coordinates to the metal center. Although these kinds of ligands have been successfully used in various asymmetric metal-catalyzed reactions,[11] only a few examples concerning their use in the rhodium-catalyzed asymmetric hydrogenation have been reported, limited to the use of diphosphites[12] or combinatorial mixtures of phosphites and phosphoramidites.[13] To the best of our knowledge, only one example using monophosphite *tropos* ligands is reported, which afforded enantiomeric excess up to 75% in the hydrogenation of dimethylitaconate.[14] Our recent finding that the cholestanic backbone is able to induce a prevalent sense of twist on the biphenyl moiety of *tropos* biphenylphosphites linked at the 12-position of the deoxycholic acid[15] has opened the possibility to obtain a new class of chiral ligands whose activity and enantioselectivity can be checked in the asymmetric rhodium-catalyzed hydrogenation. This kind of ligands has already proven to be able to promote the copper-catalyzed conjugate addition

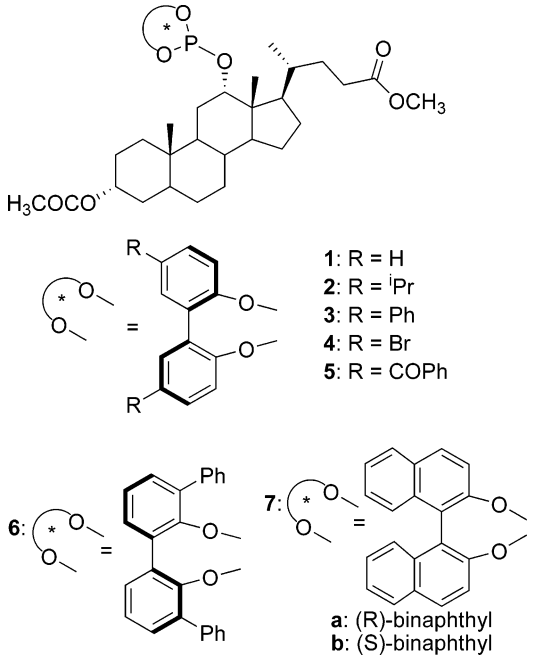

FIGURE 1. Structures of the phosphite ligands.

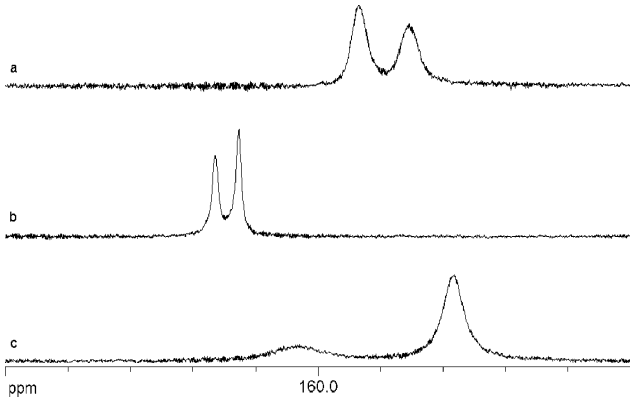

FIGURE 2. ^{31}P NMR (121 MHz) spectra of phosphite **5** in (a) toluene-d_8 and (b) THF-d_8 solutions and of (c) phosphite **6** in THF-d_8 solution, at the decoalescence temperature.

of diethylzinc to enones in enantioselective fashion.[16] The results reported herein concern the use of *tropos* deoxycholic acid derived biphenylphosphites **1**−**6** (Figure 1) in the asymmetric Rh(I)-catalyzed hydrogenation of the benchmark substrate dimethylitaconate. The use of phosphites **7** will allow us to compare the behavior of flexible and atropoisomeric analogues in order to evaluate the effectiveness of the *tropos* motif in the asymmetric induction process[17] as far as this kind of ligand is concerned. A correlation between asymmetric induction and stereochemical features of the free ligands or their rhodium complexes, aimed at gaining information about the factors governing the enantioselectivity of this class of *tropos* ligands, is also presented.

Results and Discussion

Phosphites **1**−**6** were prepared by reacting methyl-3-acetyldeoxycholate with the suitable biphenylchlorophosphite,

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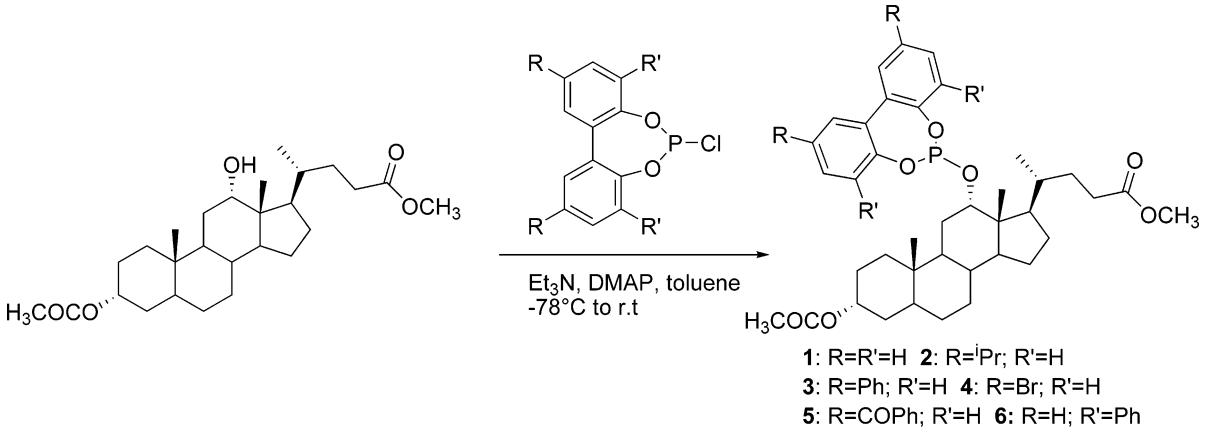
SCHEME 1. Synthesis of *tropos* Phosphites



which was in turn obtained from the corresponding biphenol and PCl_3 (Scheme 1).[15]

The *tropos* nature of phosphites **1**−**4** as well as the prevalent sense of twist of their biphenyl moiety has been already determined by circular dichroism (CD) and variable-temperature ^{31}P NMR measurements.[15,16] A correlation between the relative position of the ^{31}P NMR signals of the two diastereoisomeric species and the sense of twist of the biphenyl moiety has been also found.[16] On this basis it is possible to ascertain the prevalent sense of twist of phosphites **5** and **6** only using variable-temperature ^{31}P NMR measurements. In fact, the CD spectra of both these phosphites (Supporting Information) cannot be compared to the CD spectrum of **1**, for which a correlation between the sign of the Cotton effects and the sense of twist of the biphenyl moiety has been determined,[15] due to the presence of phenyl or benzoyl groups conjugated to the biphenyl moiety. It significantly alters the nature of the electronic transitions of the biphenyl chromophore.[18] The sole information we were able to extract from the CD measurements is the dependence of the sense of twist of the biphenyl moiety on the solvent only in the case of **5**. In passing from acetonitrile solution to THF solution, the CD signals of **5** vanish, whereas the CD spectrum of **6** remains unaltered, as far as number sign and intensity of the Cotton effects are concerned. For this reason, we measured ^{31}P NMR spectra both in THF and toluene solution for **5** and only in THF solution for **6**. The variable-temperature NMR profile of **5** (Supporting Information) confirms the presence of two diastereoisomeric species, which fast interconvert at room temperature, and shows a decoalescence temperature of 193 K both in THF and in toluene solutions (Figure 2), corresponding to an interconversion barrier for the two diastereoisomeric species of 9.7 kcal/mol.[19]

On the basis of the relative position of the ^{31}P signals at the decoalescence temperature, it is possible to attribute a M prevalent sense of twist in toluene solution and a P sense of twist in THF solution to the biphenyl moiety of **5**. An 8% prevalence of the M sense of twist in toluene and P screw sense in THF is calculated on the basis of the integrated area of the NMR signals. The variable-temperature ^{31}P NMR measurements of **6** (Supporting Information) show that a fast equilibrium at room temperature between two diastereoisomeric species is also present in this case. At room temperature, only one signal is present, which broadens on lowering the temperature and splits into two signals at 243 K (Figure 2), a decoalescence temperature corresponding to an interconversion barrier of 11.8 kcal/mol.[19] The relative position of the signals corresponding to the two diastereoisomeric species points out a P screw sense of the biphenyl moiety of the prevailing diastereoisomer. The integrated area of the two signals reveals a diastereoisomeric ratio of 70/30, the highest observed prevalence of one sense of twist for a substituted biphenylphosphite moiety linked at the 12-position of the cholestanic backbone. The high prevalence of the P sense of twist, the lack of dependence of the screw sense on the solvent, and the higher interconversion barrier are likely attributable to the presence of the two phenyl substituents at the 3,3′-positions of the biphenyl moiety, which deeply changes the stereochemical features of the phosphite.

The ligands **1**−**6**, having different substituents on the biphenyl moiety, but all having *tropos* nature and the atropoisomeric phosphites **7a,b**, were assayed in the rhodium-catalyzed enantioselective hydrogenation of dimethylitaconate, not only to check their effectiveness but also to gain information about the structural features helping the asymmetric induction. In a typical procedure, the catalytic system was generated "in situ" by reacting a solution of the Rh(I) salt and the chiral ligand in 1:2 ratio under nitrogen atmosphere for 10 min; the hydrogenation reaction was carried out at 7 bar hydrogen pressure for 20 h. The effect of different parameters on the outcome of the reaction was checked using **1** as chiral ligand, and the results are reported in Table 1.

The reaction carried out at room temperature in dichloromethane as solvent, using a 200:1 substrate/catalytic system ratio, gives the hydrogenated product in good enantiomeric excess but in low yield (entry 1). Increasing the amount of catalytic system affords quantitative yield of the hydrogenated product without affecting the stereochemical outcome of the reaction (entry 2). Lowering the reaction temperature until −10 °C does not improve the enantiomeric excess (entries 3 and 4). The use of the Rh(I) triflate affords worse results in terms of enantioselectivity (entry 5). An improvement of asymmetric induction is achieved using $Rh(cod)_2BF_4$ as catalytic precursor in dichloroethane as solvent: under these reaction conditions, a hydrogenation product in 90% ee is obtained (entry 6). The use of $Rh(cod)_2SbF_6$ gives similar results (entry 7). Therefore, because its higher solubility allows the use of different solvents, the reaction was performed in THF, the solvent wherein the sense of twist of the biphenyl moiety of **1** changes.[15] It was performed in THF in order to verify if the opposite enantiomer

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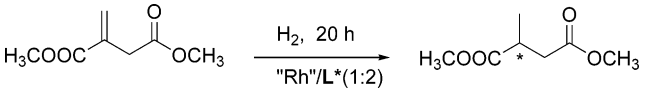
TABLE 1. Rhodium-Catalyzed Asymmetric Hydrogenation[a] of Dimethylitaconate in the Presence of Ligands 1−7



entry	L*	"Rh"	solvent	*T* (°C)	yield (%)	ee% (ac)
1	**1**	$Rh(cod)_2BF_4$	CH_2Cl_2	25	30[b]	81 (*S*)
2	**1**	$Rh(cod)_2BF_4$	CH_2Cl_2	25	100	80 (*S*)
3	**1**	$Rh(cod)_2BF_4$	CH_2Cl_2	0	100	75 (S)
4	**1**	$Rh(cod)_2BF_4$	CH_2Cl_2	−10	100	82 (S)
5	**1**	$Rh(cod)_2OTf$	CH_2Cl_2	25	100	52 (S)
6	**1**	$Rh(cod)_2BF_4$	$(CH_2)_2Cl_2$	25	100	90 (S)
7	**1**	$Rh(cod)_2SbF_6$	$(CH_2)_2Cl_2$	25	100	91 (S)
8	**1**	$Rh(cod)_2SbF_6$	THF	25	100	racemic
9	**2**	$Rh(cod)_2BF_4$	$(CH_2)_2Cl_2$	25	100	74 (S)
10	**3**	$Rh(cod)_2BF_4$	$(CH_2)_2Cl_2$	25	100	70 (S)
11	**4**	$Rh(cod)_2BF_4$	$(CH_2)_2Cl_2$	25	100	62 (S)
12	**5**	$Rh(cod)_2BF_4$	$(CH_2)_2Cl_2$	25	100	70 (S)
13	**6**	$Rh(cod)_2BF_4$	$(CH_2)_2Cl_2$	25	100	racemic
14	**7a**	$Rh(cod)_2BF_4$	$(CH_2)_2Cl_2$	25	100	68 (R)
15	**7b**	$Rh(cod)_2BF_4$	$(CH_2)_2Cl_2$	25	100	94 (S)

[a] Reaction conditions: **L*** (0.01 mmol), [$Rh(cod)_2BF_4$] (0.005 mmol), dimethylitaconate (0.5 mmol), solvent (2.5 mL), H_2 (7 bar), rt, 20 h. Yields and ee values were determined by GC equipped with a chiral capillary column (Chiraldex G-TA). Absolute configuration of the prevailing enantiomer was determined by comparison with literature data.[20] [b] A 200:1 ratio substrate/"Rh" was used.

of the hydrogenation product can be obtained, as already observed in the copper-catalyzed asymmetric conjugate addition of diethylzinc to enones.[16] Unfortunately, under these reaction conditions, a racemic product is obtained (entry 8), as observed with other kinds of phosphites.[9d] The reaction conditions affording the best results in terms of yield and enantiomeric excess of the product were used to check the activity and enantioselectivity of the other phosphites in the asymmetric hydrogenation of dimethylitaconate (Table 1). All the ligands give a catalytic system showing comparable activity, with quantitative yield of the hydrogenation product being obtained in all cases. The enantioselectivity exhibited by phosphites having substituents at the 5,5′-positions of the biphenyl moiety is scarcely dependent on the nature of the substituent, with the enantiomeric excess values ranging from 70 to 74% (entries 9, 10, and 12) except in the case of **4**, which gives only 62% ee of the hydrogenated product (entry 11). On the contrary, substitution at the 3,3′-positions of the biphenyl moiety is detrimental to the asymmetric induction: using phosphite **6**, a racemic product is obtained (entry 13). All phosphites give an *S* configured prevailing enantiomer. Phosphites **7a** and **7b** bearing an *R* and *S* atropoisomeric binaphthyl moiety, respectively, afford enantiomeric hydrogenation products (entries 14 and 15), suggesting that, as observed with other types of phosphites,[7,9d] the sense of asymmetric induction depends on the absolute configuration of the biaryl moiety. In addition, the higher value of asymmetric induction obtained using **7b** suggests that the (*S*)-binaphthylphosphite moiety linked at the 12-position of deoxycholic acid constitutes the matched pair for this reaction. Given that the M sense of twist corresponds to the *R* absolute configuration, this result should indicate that the biphenyl moieties of phosphites **1**−**5** are twisted in the "wrong" sense. However, this does not explain why **6**, whose biphenyl moiety is twisted in a P sense, gives a racemic product. In addition, the sense of asymmetric induction of **7a** is different from that of **1**−**5**. This can be attributed to a change of the screw sense

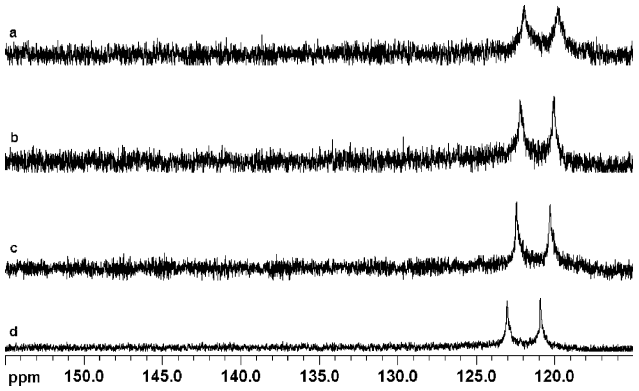


FIGURE 3. ^{31}P NMR (121 MHz) spectra of 1:2 $Rh(cod)_2BF_4$/**2** mixture in CD_2Cl_2 solution at (a) 298 K, (b) 273 K, (c) 233 K, and (d) 213 K.

of the biphenyl moiety of **1**−**5** in passing from the free ligand to the coordinated species or to a different mechanism of asymmetric induction in passing from *tropos* to atropoisomeric ligands. In this last case, the matched pair of *tropos* phosphites could be different from that of atropoisomeric analogues. The asymmetric induction results obtained with the *tropos* ligands are surprising if the extent of the prevalence of one sense of twist for the biphenyl moiety of each phosphite is taken into account. In fact, phosphite **6**, showing the highest prevalence, is that one affording the racemic product, whereas an 8% of prevalence in the case of phosphite **5** corresponds to the achievement of a product in 70% ee. These results clearly show that the extent of the prevalence of one sense of twist of the biphenyl moiety in the free ligand is not a stereochemical feature directly correlated to the extent of asymmetric induction. Therefore, to shed further light on the nature of the catalytic species, we performed ^{31}P NMR measurements on the catalytic precursor obtained starting from phosphite **2**, which shows a low prevalence of one sense of twist of its biphenyl moiety[16] but affords good asymmetric induction, and **6**, which gives a racemic product although its biphenyl moiety shows the highest prevalence of one screw sense. The NMR measurements were performed on a dichloromethane solution of 1:2 mixture of $Rh(cod)_2BF_4$/phosphite because hydrogenation reactions were performed using this ratio and on the basis of the proved hypothesis that the catalytically active species has two phosphite ligands coordinated to the metal.[21] The ^{31}P NMR spectrum of the $Rh(cod)_2BF_4$/**2** mixture (Figure 3) recorded at room temperature shows the presence of a broad doublet signal at 121 ppm with the typical coupling constant Rh−P (J = 263 Hz), which sharpens on lowering the temperature until 213 K (decoalescence temperature for the signals of the free ligand), but does not undergo any doubling.

Given that the interconversion barrier between the M and P diastereoisomeric forms of *tropos* ligands becomes higher once they are complexed to the metal center,[22] the presence of the doublet in the ^{31}P NMR spectrum that does not undergo doubling on lowering the temperature is likely due to the formation of only one species, where the biphenyl moieties of

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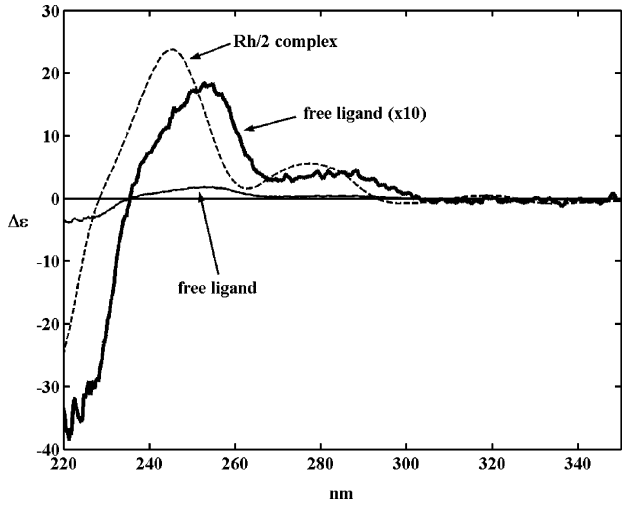

FIGURE 4. CD spectra of phosphite **2** in acetonitrile solution and 1:2 $Rh(cod)_2BF_4$/**2** mixture in CH_2Cl_2 solution.

both the coordinated ligands are twisted in the same highly prevalent screw sense. The sense of twist of the biphenyl moieties of the two ligands cannot be different because, in that event, two different signals would be present in the spectrum, each having a double doublet multiplicity, since the phosphorus atoms of the two ligands would be heterotopic, giving rise to different signals, with multiplicity due to the P−P and P−Rh coupling. In addition, no signals are present in the spectral region where the resonances of the free ligand are found, suggesting that the ligand is totally complexed to the metal center. Given that the NMR data show the presence in solution of only one complexed species, it is possible to use CD spectroscopy in order to determine the sense of twist of the biphenyl moiety of the complexed species and hence to gain information about the reason why the sense of asymmetric induction changes in passing from atropoisomeric to *tropos* ligands. The CD spectrum of the 1:2 $Rh(cod)BF_4$/**2** mixture, normalized to ligand concentration, shown in Figure 4 in comparison to that of **2**, is very similar to the CD spectrum of the free ligand as far as number and sign of the Cotton effects are concerned; the blue shift of the biphenyl CD bands in the complex can be attributed both to the complexation of phosphorus to the Rh center and to the different solvents where the measurements were carried out. The most evident difference between the two CD spectra is the intensity of the Cotton effects that is remarkably higher in the spectrum of the complex than in the spectrum of the free ligand.

The similarity of the two spectra suggests that the biphenyl moiety has in the complexed species the same sense of twist as in the free ligand, whereas the higher intensity of the Cotton effects in the spectrum of the complex is attributable to the formation of only one species, as indicated by the NMR measurements, wherein the biphenyl moieties assume a totally prevalent M screw sense. Two different interpretations[10,17] for the formation of only one complexed species are possible, both related to the *tropos* nature of **2**. According to the first one, the M diastereoisomer is the species coordinating preferentially to the metal center, and this causes shift of the M−P equilibrium of the free ligand toward the M form, so that only the complex containing the M diastereoisomeric ligand is formed. According to the second one, both diastereoisomeric complexed species in equilibrium between each other are formed, but the equilibrium is rapidly shifted toward the most stable form. In any case, the formation of only one species wherein both coordinated ligands possess M twisted biphenyl moieties suggests that the different sense of asymmetric induction shown by *tropos* phosphites **1**−**5** with respect to atropoisomeric ligands **7a,b** is only due to a change in the asymmetric induction mechanism.

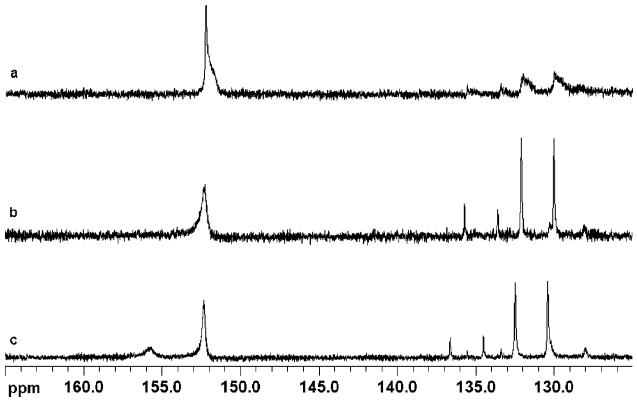

FIGURE 5. ^{31}P NMR (121 MHz) spectra of 1:2 $Rh(cod)_2BF_4$/**6** mixture in CD_2Cl_2 solution at (a) 308 K, (b) 298 K, and (c) 233 K.

The ^{31}P NMR spectrum of the $Rh(cod)_2BF_4$/**6** mixture at room temperature (Figure 5) shows the presence of two doublet signals at 131 ppm (J = 242 Hz) and at 134 ppm (J = 258 Hz) and a singlet at 152 ppm. On lowering the temperature, the singlet broadens and, at 233 K, doubles in two signals at 152 and 155 ppm, whereas the two doublets remain unchanged.

The signal at 152 ppm is attributable to the resonance of the free ligand, whereas the two doublets are likely the signals of two different rhodium complexes. On the basis of the integrated areas of the signals, a 45:55 ratio between free ligand and complexed species and a 70:30 ratio between the two rhodium complexes were calculated. Therefore, an incomplete complexation of the ligand to the rhodium center can be inferred, probably due to the steric hindrance exerted by the two phenyl ring at the 3,3′-positions of the biphenyl moiety on the phosphorus atom, which prevents complexation to some extent. The amount of complexed ligand originates two species where the phosphorus atoms are homotopic, as the multiplicity of the NMR signals suggests, and hence the two biphenyl units of each complex have the same sense of twist. This means that the two species derive from the complexation of the two M and P diastereoisomers of phosphite **6**; this hypothesis seems to be confirmed by the NMR measurements at 308 K (Figure 5), where the two doublets broaden and approach each other, a typical behavior for species which are in a slow equilibrium that become faster when the temperature is increased. The formation of two diastereoisomeric species after complexation of **6** is probably attributable to the higher interconversion barrier between the M and P forms of free **6**, which implies a higher interconversion barrier also for the complexed ligands, preventing shift of the equilibrium between M and P diastereoisomers toward the most stable species; this is possible in the case of **2** by virtue of its lower interconversion barrier. These NMR data suggest a possible rationalization for the different enantioselectivity shown by **2** and **6**. In fact, the reaction between **2** and $Rh(cod)_2BF_4$ gives rise to the quantitative formation of a diastereomerically pure complex, whereas **6** is only partly bound to the rhodium center generating two diastereoisomeric complexes in a ratio similar to that observed for the two diastereoisomers of the free ligand. It is conceivable that in the case of this kind of ligands, unlike as observed in other cases,[13] none of the possible complexes has higher activity and enantiose-

lectivity, so that the formation of more complexed species in lower amount results in worsening of the stereochemical outcome of the reaction.

Conclusions

The use of *tropos* phosphites **1**−**6** in the rhodium-catalyzed asymmetric hydrogenation of dimethylitaconate has proven that the *tropos* motif is a stereochemical feature affording good deoxycholic acid based phosphite ligands. In fact, the hydrogenation product is obtained with enantiomeric excesses up to 91%, a comparable value to the asymmetric induction obtained using one of the atropoisomeric binaphthylphosphite analogues. The comparison between *tropos* and atropoisomeric deoxycholic acid based phosphites has revealed that the sense of asymmetric induction depends on the absolute configuration of the biaryl moiety, and it is different for *tropos* and atropoisomeric ligands. The stereochemical outcome of the hydrogenation reactions demonstrates that the extent of the prevalence of one sense of twist of the biphenyl moiety in free ligands is not correlated to the extent of asymmetric induction. Variable-temperature ^{31}P NMR measurements on Rh complexes of some phosphites have allowed us to conclude that the extent of asymmetric induction depends on the formation of only one complexed species, which is in turn guaranteed by a low interconversion M−P barrier for the biphenyl moiety joined to a little steric hindrance around the phosphorus atom. CD measurements on the Rh−phosphite complex have revealed that the biphenyl moiety of the complexed species has the same sense of twist as in the free ligand. This result allows us to conclude that the change of the sense of asymmetric induction from atropoisomeric to *tropos* ligands is attributable to a change in the enantioselection mechanism, and as a consequence, this suggests that different matched and mismatched pairs are found for the two classes of phosphites.[23] In other words, the prevalence of the M sense of twist of the biphenyl moiety, guaranteed by a suitable substitution, is a stereochemical feature making these *tropos* phosphites good asymmetric rhodium ligands.

Experimental Section

General experimental details can be found in the Supporting Information.

5,5′-Dibenzoyl-2,2′-dihydroxybiphenyl. Dry DMF (4 mL) was dropwise added to $AlCl_3$ (23 g, 0172 mol). The mixture was warmed to 35 °C, then a solution of biphenol (2 g, 11 mmol) in benzoyl chloride (3.5 mL, 30 mmol) was added. The reaction mixture was warmed to 85 °C and stirred at that temperature for 5 h, then, after cooling to room temperature, a 10% HCl solution was added and the aqueous phase was extracted with diethyl ether (3 × 15 mL). The collected organic phases were dried on anhydrous Na_2SO_4, then concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, CH_2Cl_2/acetone 90:10) affording 1.4 g of pure product (3.5 mmol, 33%) as a solid: mp 230 °C; ^{1}H NMR (200 MHz, $CDCl_3$, δ) 5.00 (s, 2H), 6.63 (d, J = 8.4 Hz, 2H), 6.99−7-36 (m, 14H); ^{13}C NMR (50 MHz, $CDCl_3$, δ) 120.9, 129.6, 133.0, 133.4, 134.4, 136.4, 136.6, 139.6, 143.3, 164.2, 199.9; IR (KBr, cm^{-1}) 3111, 1694, 1638, 1588, 1566, 1500,; 1383, 1283, 1144, 1111, 922, 833, 716, 616. Anal. Calcd for $C_{26}H_{18}O_4$: C, 79.17; H, 4.60; O, 16.23. Found: C, 79.22; H, 4.58.

Preparation of the Phosphites: Representative Procedure. A warm solution (60 °C) of biphenol (2.05 mmol) in dry toluene or THF (25 mL) was slowly added to a solution of PCl_3 (2.05 mmol) and Et_3N (4.1 mmol) in dry toluene or THF (5 mL). After 2 h of stirring, the reaction mixture was filtered under argon atmosphere. The solution was dropwise added to a solution of DMAP (2.23 mmol) and Et_3N (7.3 mmol) in dry toluene or THF (25 mL) at −60 °C over 2 h, then methyl-3-acetyldeoxycholate (2.1 mmol) was added, and the mixture was 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 (SiO2, CH_2Cl_2/acetone, 97:3), affording the pure phosphite.

Methyl 3α-Acetyloxy-12α-(5,5′-dibenzoylbiphenyl-2,2′-diyl)-phosphite-5β-cholan-24-oate 5: 0.6 g (0.69 mmol, 39%); mp 97−100 °C; $[\alpha]^{22}_D$ = 25.3 (c = 1.02, CH_2Cl_2); ^{1}H NMR (200 MHz, benzene-d_6, δ) 0.49 (s, 3H), 0.91 (s, 3H), 1.08 (d, J = 6.0 Hz, 3H), 1.20−2.00 (m, 25H), 1.70 (s, 3H), 2.22−2.31 (m, 1H), 3.36 (s, 3H), 4.26 (m, 1H), 4.63 (m, 1H), 6.91−7.14 (m, 10H), 7.29 (d, J = 8.4 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 7.8 Hz, 2H),7.85 (m, 2H); ^{13}C NMR (50 MHz, benzene-d_6, δ) 12.2, 17.8, 20.8, 22.9, 23.5, 26.0, 26.8, 27.0, 27.6, 28.8, 30.9, 31.1, 32.4, 33.6, 34.2, 35.0, 35.8, 41.7, 46.6, 46.7, 47.8, 50.9, 73.7, 79.4 (d, ^2J = 17.1 Hz), 122.5, 128.1, 129.9, 131.4, 131.9, 132.6, 135.2, 135.3, 137.8, 153.3, 169.5, 173.5, 193.9, 198.1; ^{31}P NMR (121 MHz, benzene-d_6, δ) 161.6; IR (KBr, cm^{-1}) 2940, 2861, 2353, 1734, 1655, 1598, 1484, 1445, 1362, 1318, 1252, 1108, 1028, 963, 884, 805, 696. Anal. Calcd for $C_{51}H_{55}O_9P$: C, 72.67; H, 6.58; O, 17.08; P, 3.67. Found: C, 74.20; H, 6.49; P, 3.75.

Methyl 3α-Acetyloxy-12α-(3,3′-diphenylbiphenyl-2,2′-diyl)-phosphite-5β-cholan-24-oate 6: 0.53 g (0.65 mmol, 32%); mp 69−71 °C; $[\alpha]^{21}_D$ = −24.20 (c = 1.08, CH_2Cl_2); ^{1}H NMR (300 MHz, benzene-d_6, δ) 0.28 (s, 3H), 0.58 (s, 3H), 0.60 (d, J = 6.6 Hz, 3H), 1.00−1.72 (m, 25H), 1.78 (s, 3H), 1.90−2.10 (m, 1H), 3.35 (s, 3H), 4.65 (m, 1H), 4.85 (m, 1H), 7.30−7.58 (m, 16H); ^{13}C NMR (75 MHz, benzene-d_6, δ) 12.1, 17.6, 17.7, 21.0, 23.0, 23.4, 25.9, 26.4, 27.2, 27.6, 30.9, 31.0, 32.6, 33.5, 34.0, 34.9, 35.1, 35.9, 42.0, 45.8, 46.1, 46.2, 47.1, 50.7, 74.2, 76.5 (d, ^2J = 17.5 Hz), 124.9, 125.0, 129.6, 129.8, 129.9, 130.5, 130.6, 132.8, 133.4, 135.0, 135.1, 138.4, 138.5, 146.7 (d, ^2J = 5.5 Hz), 147.1 (d, ^2J = 6.0 Hz), 165.9, 173.8; ^{31}P NMR (121 MHz, benzene-d_6, δ) 150.3; IR (KBr, cm^{-1}) 2933, 2855, 1727, 1450, 1416, 1377, 1361, 1244, 1183, 1077, 1022, 888, 855, 761, 700. 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.

General Procedure for the Rh-Catalyzed Asymmetric Hydrogenation. A solution of the Rh(I) salt (0.005 mmol) and the phosphite (0.01 mmol) in dry solvent (2.5 mL) was introduced in a stainless steel autoclave and stirred for 10 min. Dimethylitaconate (0.5 mmol) was then added; the autoclave was closed and filled with hydrogen (7 bar). After 20 h of stirring, the autoclave was opened and the reaction mixture, after filtration over a pad of silica gel, was analyzed by chiral GC for conversion and enantiomeric excess determination.

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Supporting Information Available: General experimental details, copy of ^{1}H NMR spectra of **5**, **6**, and 5,5′-dibenzoyl-2,2′-dihydroxybiphenyl, CD spectra of **5** and **6**, and variable-temperature ^{31}P NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org

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(23) In the examples reported in the literature concerning the use of binaphthyl-based phosphites and phosphoramidites (see ref 9) in the hydrogenation of dimethylitaconate, the (*R*)-binaphthyl moiety induces the formation of an *S* product; by contrast, the use of *R atropos* biphenyl-based phosphites (ref 9d) gives an *R* product. These results suggested a different induction mechanism for the two kinds of ligands. Our results, obtained using *tropos* and *atropos* ligands having the same configurationally stable structural motif (cholestanic backbone), strongly point out the different asymmetric induction mechanism for *tropos* biphenyl-based phosphites and *atropos* binaphthyl-based phosphites.