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Catalytic enantioselective conjugate addition of dialkyl zinc reagents to α,β -unsaturated ketones mediated by new phosphite ligands containing binaphthalene/1,2-diphenylethane moieties: a practical synthesis of (R)-(-)-muscone

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Abstract—New diastereoisomeric phosphites based on either (R)- or (S)-2,2'-dihydroxy-1,1'-binaphthyl (BINOL) and having the chiral alcoholic moiety derived from the monobenzyl ether of (R,R)-1,2-diphenylethane-1,2-diol have been prepared and used as chiral ligands in the enantioselective copper-catalyzed 1,4-addition of diethylzinc to chalcone and 2-cyclohexen-1-one (enantiomeric excesses up to 48%). With the (aR,R,R) ligand dimethylzinc adds enantioselectively to (E)-cyclopentadecen-2-en-1-one to give (R)-(–)-muscone (68% yield, 78% ee). This provides an efficient access to a valuable ingredient of the perfume industry. However, with the (aS,R,R) ligand, (S)-(+)-muscone is obtained with longer reaction times (37% yield and 10% ee) with a very high double diastereoselection effect being observed.

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1. Introduction

Over the last few years, significant progress in the field of the catalytic asymmetric conjugated addition of organozinc compounds to α,β -unsaturated ketones has been made.¹ This process allows the construction of C-C bonds in high chemical yields with efficient stereocontrol, thus providing synthetic organic chemistry with a very useful tool to assemble large and polyfunctional molecules.² The success obtained in such a process relies mainly in the development of efficient catalytic precursors which are constituted by Cu(II) or Cu(I) salts coordinated by enantiopure phosphorus ligands, i.e. phosphites³ and phosphoroamidites.⁴ In these ligands the chiral source is often derived from enantiopure 2,2'-dihydroxy-1,1'-binaphthyl, BINOL, or modified binaphthols, coupled to another chiral residue, so the phenomenon of double asymmetric induction results.⁴

Stimulated by recent literature reports, we reasoned that a new family of enantiopure phosphite compounds

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could be prepared by coupling the diol framework of BINOL with a second enantiopure alcoholic moiety obtained by a simple monoether of 1,2-diphenylethane-1,2-diol 1 (Fig. 1), i.e. a type of compound already employed as a chiral controller.⁶

Herein we report the synthesis of the diastereomeric phosphites **3a** and **3b** (Fig. 1) and their application as chiral controllers in the asymmetric conjugated addition of diethylzinc to chalcone and 2-cyclohexen-1-one, assumed as model compounds of acyclic and cyclic ketones. In addition, the asymmetric conjugate addition of dimethylzinc to (*E*)-cyclopentadec-2-en-1-one is also reported in order to provide a new, practical catalytic process^{2a,7} for the synthesis of (*R*)-(–)-muscone, a rare and valuable perfumery ingredient isolated from the male musk deer *Moschus moschiferus*.

2. Results and discussion

2.1. Synthesis of phosphites

The two novel enantiomerically pure phosphites 3a and 3b were synthesized by treating chlorophosphite 2, prepared by starting from monobenzyl ether of (R,R)-1,2-

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Figure 1. Structure of alcohol (R,R)-1 and phosphite derivatives.

diphenylethane-1,2-diol **1** and PCl₃, with (*R*)- or (*S*)-BINOL **4**, in the presence of triethylamine and DMAP (Scheme 1). The monobenzylether of (*R*,*R*)-1,2diphenylethane-1,2-diol **1** can easily be prepared, as previously reported,^{6a,b} from enantiopure (*R*,*R*)-1,2diphenylethane-1,2-diol.⁸

2.2. Asymmetric conjugate reactions

The effectiveness of this novel catalytic system was first tested by studying the conjugate addition of diethylzinc on chalcone and 2-cyclohexen-1-one. In a typical procedure the catalytic system was generated in situ by stirring a toluene solution containing the ligand, **3a** or **3b**, and the copper salt, $Cu(OTf)_2$, for 1 h at room temperature. The additions of diethylzinc to chalcone and to 2-cyclohexen-1-one were carried out in toluene at -40° C, using 3 mol% of the catalyst with a molar

ratio 1:2 between $Cu(OTf)_2$ and the chiral ligand **3a** or **3b**. The results obtained are shown in Table 1 for chalcone and in Table 2 for 2-cyclohexen-1-one.

As far as the addition to chalcone was concerned, we saw that both 3a and 3b acted as efficient catalytic precursors of the conjugate addition. In fact, the products were obtained in short reaction times with satisfactory yields (in both cases the presence of a secondary product obtained by the Michael addition of the resulting zinc enolate to the starting enone was observed while the 1,2-adduct was not detected). However, the diastereoisomeric relationship between the two ligands had a clear effect on stereoselection. In fact, the (aR,R,R) ligand gave the (S)-stereoisomer with 48% e.e. (entry 1) and the (aS, R, R) ligand gave (R) with 11% e.e. (entry 2). The stereochemical outcome was clearly determined by the BINOL moiety: 3a derived from (R)-BINOL induced the formation of the (S)product, whilst **3b**, derived from (S)-BINOL, induced the formation of the (R)-product. This is a well-known behavior concerning these types of ligands.¹ As far as the results obtained in the catalytic 1,4-addition of diethylzinc to cyclohexenone (Table 2) it is interesting to note that both 3a and 3b acted as very efficient catalytic precursors of this conjugate addition even if the stereoselectivity values obtained were unsatisfactory in both cases, i.e. no double diastereoselection was observed in this case.

The shortest route to synthesize the (R)-(-)-muscone is the enantioselective addition of a methyl group to



Scheme 1.

Table 1. Catalytic conjugate addition of diethylzinc to chalcone



Entry	Ligand	Cu(OTf) ₂ (mol%)	Cu(OTf) ₂ /L*	T (°C)	Time (h)	Yield ^a (%)	E.e. ^{b,c} (%)
1	aR,R,R	3	1:2	-40	1.30	66	48 (S)
2	aS,R,R	3	1:2	-40	1.30	61	11 (<i>R</i>)

^a Isolated product.

^b Determined by HPLC analyses: Daicel Chiralcel OJ, hexane/2-propanol 99.5:0.5, 1 mL/min., $\lambda = 254$ nm, $t_r = 18.0$ (S), $t_r = 25.0$ (R).

^c Absolute configuration assigned by the sign of the optical rotation.

Table 2. Catalytic conjugate addition of diethylzinc to 2-cyclohexen-1-one

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			7	8					
Entry	Ligand	Cu(OTf) ₂ (mol%)	Cu(OTf) ₂ /L*	T (°C)	Time (h)	Yield ^a (%)	E.e. ^{b,c} (%)		
1	aR,R,R	3	1:2	-40	2	98	19 (<i>R</i>)		
2	aS,R,R	3	1:2	-40	2	98	12 (<i>S</i>)		

^a Isolated product.

^b Determined by HPLC analyses after derivatization with (*R*,*R*)-1,2-diphenylethane-1,2-diol: Daicel Chiralcel OD, hexane/2-propanol 99.7:0.3, 0.5 mL/min., $\lambda = 254$ nm, $t_r = 8.0$ (*R*,*R*,*R*), $t_r = 10.0$ (*S*,*R*,*R*).

^c Absolute configuration assigned by the sign of the specific rotation.

(*E*)-cyclopentadec-2-en-1-one, since this unsaturated 15-membered ketone can be readily prepared from commercially available cyclopentadecanone.⁹ As a result, we have focused our attention on the catalytic conjugate addition of dimethylzinc to (*E*)-cyclopentadec-2-en-1-one **9**, using the new phosphites **3a** and **3b**. The results are shown in Table 3.

The data collected in Tables 1-3 deserves some comments: first of all it is interesting to observe that substrates 5 and 9 give rise to lower chemical yields of products 6 and 10, respectively, than substrate 7. Additionally, in the crude reaction mixture, by-products derived from the addition of the zinc enolate to the starting ketone (in the cases of 5 and 9) as well as 1,2-addition product (only for 9) can be detected. The similar behavior of 5 and 9 can be related to the fact that for both of them s-cis and s-trans conformers are possible whilst 7 is fixed in an s-trans-structure (see, for instance, Ref. 1c). However, the most important practical result is that of **3a** (entry 1 of Table 3), which works as an efficient catalytic precursor in the conjugate addition of dimethylzinc to 9, providing a new route to (-)-muscone. It is noteworthy that only few methods of this type are known^{2a,7} for the synthesis of (–)-muscone:

3a is clearly a more easily prepared (and thus more useful from a practical point of view) than the ligands described in the references.^{2a,7} In addition, a remarkable difference in behavior between **3a** and **3b** is seen: in practice, **3b** is not even capable in promoting the reaction; in fact (+)-muscone is obtained in low chemical yield with a very unsatisfactory enantiomeric excess. Of course, such difference in double stereoselection requires further, detailed studies.

3. Conclusions

Herein the asymmetric 1,4-addition of dialkylzinc reagents to α,β -unsaturated ketones using, as chiral promoters, new diastereoisomeric phosphites derived from (*R*)- or (*S*)-2,2'-dihydroxy-1,1'-binaphthalene and (*R*,*R*)-1,2-diphenylethane-2-benzyloxyethanol, has been described. The most significant results are as follows: with the (a*R*,*R*,*R*) ligand, (*R*)-(–)-muscone, the key flavor component of musk, is obtained in 68% yield and 78% ee, whilst the (a*S*,*R*,*R*) ligand did not even promote the reaction. It should be noted that (+)-muscone was obtained after much longer reaction times at higher temperatures, but with a poor yield and ee. It is also

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Table 3. Catalytic conjugate addition of dimethylzinc to (E)-cyclopentadec-2-en-1-one

		9		10			
Ligand	Cu(OTf) ₂ (mol%)	Cu(OTf) ₂ /L*	T (°C)	Time (h)	Yield ^a (%)	E.e. ^b (%)	
aR,R,R aS,R,R	3 3	1:2 1:2	-10 0	2 20°	68 37	78 (<i>R</i>) 10 (S)	

0

^a Isolated product.

Entry

1 2

^b Determined by specific rotation measurements [lit.¹⁰: for (*R*)-(–)-muscone [α]_D = –11.7 (*c* 0.8, MeOH)].

^c The reaction does not work at -10° C, significant (10–15%) amounts of the addition product of the resulting zinc enolate to 9 and of the 1,2-addition product are found.

important to see that the results present interesting implications for both the practical and theoretical points of view. In practice a new, convenient access (which uses simply-to-be-prepared, cheap ligands) has been provided to this important ingredient of the perfume industry: the achievement of higher yields and ees can be related to a suitably designed monoether of (R,R)-1,2-diphenylethane-1,2-diol. From the theoretical point of view, the huge dependence of the chemical and stereochemical outcome of the reaction on the absolute configuration of the ligand, constitutes an aspect deserving detailed experimental and computational studies. Hopefully, its understanding will provide a fundamental contribution to the comprehension of the mechanism of this important reaction.

4. Experimental

4.1. General

¹H and ¹³C NMR spectra were recorded in CDCl₃ on a Bruker Aspect 300 MHz NMR spectrometer, using TMS as the external standard. 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-1580 intelligent HPLC pump equipped with a Varian 2550 UV detector. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. Melting points were taken using a Kofler Reichert-Jung Thermovar apparatus and are uncorrected. Toluene and dichloromethane were refluxed over sodium-benzophenone and calcium hydride, respectively, and distilled before the use. Unless otherwise specified the reagents were used without any purification. (1R, 2R)-1,2-Diphenyl-2-benzyloxyethanol 1^{6a,b} and cyclopentadec-2-en-1-one⁹ were obtained according to literature procedures.

4.2. Synthesis of phosphites (aR,R,R)-3a and (aS,R,R)-3b

A solution of (1R,2R)-1,2-diphenyl-2-benzyloxyethanol (552 mg, 1.8 mmol) in toluene (5 mL) was added in 15 min to a cooled solution (-60°C) of freshly distilled phosphorus trichloride (157 µL, 1.8 mmol) and triethylamine (1.3 mL, 9 mmol) in toluene (3 mL). The reaction mixture was stirred at -60°C for 2 h. Then, to the reaction mixture was added DMAP (240 mg, 1.96 mmol) and, dropwise, a solution of (*R*) or (*S*)-BINOL (515 mg, 1.8 mmol) in toluene (14 mL). The reaction mixture was stirred at -60°C for 2 h and then at rt for 20 h. The reaction was monitored by TLC. The reaction mixture was filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO₂, CH₂Cl₂), affording the pure phosphite as white solid.

(aR,R,R)-**3a**: (38%); $[\alpha]_D = -246$ (*c* 0.55, CHCl₃). Mp: 107–110°C; ¹H NMR (300 MHz, CDCl₃): δ 4.48 (part A of AB system, 1H, J = 11.7 Hz), 4.49 (d, 1H, J = 8.1

Hz), 4.53 (part B of AB system, 1H, J=11.7 Hz), 5.42 (dd, 1H, $J_1=8.8$ Hz, $J_2=8.1$ Hz), 6.81 (d, 1H, J=8.7Hz), 6.93 (d, 2H, J=7.2 Hz), 7.06 (d, 2H, J=6.4 Hz), 7.1–7.4 (m, 18H), 7.72 (d, 1H, J=9.0 Hz), 7.8–7.9 (m, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 70,97, 81.46, 85.91, 121.95, 122.57, 124.68, 124.91, 125.69, 126.10, 127.03, 127.09, 127.39, 127.53, 127.67, 127.72, 127.95, 128.08, 129.24, 128.28, 129.20, 130.06, 131.19, 131.49, 132.63, 132.86, 137.30, 137.55, 138.46, 147.70, 148.23.

(*aS*,*R*,*R*)-**3b**: (50%); $[\alpha]_D = +221$ (*c* 0.53, CHCl₃). Mp: 98–100°C; ¹H NMR (300 MHz, CDCl₃): δ 4.50 (part A of AB system, 1H, *J*=11.7 Hz), 4.56 (part B of AB system, 1H, *J*=11.7 Hz), 4.64 (d, 1H, *J*=7.5 Hz), 5.43 (dd, 1H, *J*₁=7.8 Hz, *J*₂=7.5 Hz), 6.90 (d, 1H, *J*=7.5 Hz), 7.06 (d, 2H, *J*=8.0 Hz), 7.1–7.5 (m, 20H), 7.69 (d, 1H, *J*=9.0 Hz), 7.9–8.0 (m, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 70.98, 81.18, 85.42, 122.30, 122.41, 124.93, 125.19, 126.16, 126.38, 127.30, 127.71, 127.80, 127.90, 128.04, 128.22, 128.34, 128.53, 129.72, 130.40, 131.72, 133.07, 137.48, 138.03, 138.31, 147.60.

4.3. Enantioselective conjugate addition of diethylzinc to chalcone

A solution of Cu(OTf)₂ (5 mg, 0.014 mmol, 3.0 mol%) and the chiral ligand (17 mg, 0.028 mmol, 6.0 mol%) in toluene (3 mL) was stirred for 1 h at rt under nitrogen atmosphere. To this catalyst solution chalcone (96 mg, 0.46 mmol) was added and, after cooling to -40° C, diethylzinc (1 mL, 2 equiv.) was added dropwise. The reaction was monitored by TLC. After stirring for 90 min at -40° C the reaction mixture was poured in 10 mL of 1 M HCl solution and extracted three times with diethyl ether. The combined organic phases were washed with brine, dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO₂, petroleum ether/diethylether 8:2), affording pure 1,3-diphenyl-pentanone.

4.4. Enantioselective conjugate addition of diethylzinc to 2-cyclohexen-1-one

A solution of Cu(OTf)₂ (5 mg, 0.014 mmol, 3.0 mol%) and the chiral ligand (17 mg, 0.028 mmol, 6.0 mol%) in toluene (3 mL) was stirred for 1 h at rt under nitrogen atmosphere. The solution was cooled to -40°C and 2-cyclohexen-1-one (44 mg, 0.46 mmol) followed by Et_2Zn (1 mL, 2 equiv.) were added slowly. The reaction was monitored by GC-MS. After stirring for 2 h at -40°C, the reaction mixture was poured into 10 mL of 1 M HCl solution and extracted three times with diethyl ether. The combined organic phases were washed with brine, dried with anhydrous Na₂SO₄ and filtered. Removal of the diethyl ether under reduced pressure, 700-350 mbar, at rt yielded the crude product in toluene, which was purified by flash column chromatography (SiO₂, pentane/diethylether 5:1) to afford 3-ethylcyclohexan-1-one (98%) as a colorless liquid. The e.e. was determined by HPLC analysis after derivatization with (R,R)-1,2-diphenyletan-1,2-diol. To a solution of 3-ethylcyclohexan-1-one (67 mg, 0.53 mmol)

in CH₂Cl₂ (13 mL), activated 4 Å molecular sieves were added, followed by (*R*,*R*)-1,2-diphenyletan-1,2diol (137 mg, 0.64 mmol) with traces of *p*-toluensulfonic acid. The reaction was monitored by GC/MS. After stirring for 2 h at rt the 4 Å molecular sieves were removed by filtration. The reaction mixture was dried with anhydrous Na₂SO₄, filtered and the solvent removed under reduced pressure. The crude product was purified by column chromatography (petroleum ether /diethylether 98:2) to afford the ketal of 3-ethylcyclohexan-1-one as a colorless liquid. The e.e. was determined by HPLC analysis: Daicel Chiralcel OD, hexane/2-propanol 99.7:0.3, 0.5 mL/min., λ =254 nm, t_r =8.0 (*R*,*R*,*R*), t_r =10.0 (*S*,*R*,*R*).

4.5. Enantioselective conjugate addition of dimethylzinc to 2-cyclopentadecen-1-one

A solution of Cu(OTf)₂ (5.4 mg, 0.015 mmol, 3.0 mol%) and the chiral ligand (18.5 mg, 0.03 mmol, 6.0 mol%) in toluene (5 mL) was stirred for 1 h at rt under nitrogen atmosphere. After cooling to -10° C, Me₂Zn (0.4 mL, 1.5 equiv.) was added followed by a solution of 2-cyclopentadecen-1-one (111 mg, 0.5 mmol) in toluene (1 mL). The reaction was monitored by GC/MS analysis. After stirring for 2 h at -10°C to the reaction mixture was added 10 mL of 1 M HCl solution and 5 mL of diethyl ether, which was left to stir for a few minutes. The solution was then extracted three times with diethyl ether. The combined organic phases were washed with brine, dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO₂, petroleum ether/diethylether 95:5), affording (-)-muscone (68%) as colorless oil. $[\alpha]_D = -9.2$ (c 0.95, MeOH).

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