Asymmetric Addition of Dimethylzinc to Alkylidenmalonates Mediated by Phosphorous Ligands: A New Synthetic Route to Floral Fragrances

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Contribution to the Carlo Rosini Special Issue

ABSTRACT Six new phosphite ligands were prepared and their efficiency as chiral ligands was investigated in the copper-catalyzed asymmetric conjugate addition of dimethylzinc to diethyl 3-phenylpropylidenmalonate (**5**), affording the addition product with ees up to 74%. Moreover, a simple and straightforward route to floral fragrances Phenoxanol, Citralis, and Nitrile Citralis in optically active form through the above cited reaction was proposed. *Chirality 23:761–767, 2011.* © 2011 Wiley-Liss, Inc.

KEY WORDS: asymmetric conjugate addition; phosphorous ligands; chiral esters; Phenoxanol; Citralis; Nitrile Citralis

INTRODUCTION

The copper-catalyzed conjugate addition of organozinc reagents to α,β-unsaturated carbonyl compounds is a widely used strategy for the catalytic asymmetric C—C bond formation. To this end, different types of α,β-unsaturated ketones and nitroalkenes have been used[1–4] as well as, more recently, sulfones[5,6] and aldehydes.[7] In the latter case, good enantioselectivity was achieved but with moderate to good 1–4 regioselectivity in comparison with the competitive 1–2 addition and the aldol reaction. Acyclic α,β-unsaturated esters are generally not reactive toward dialkylzinc reagents, but a few examples have been reported about the asymmetric conjugate addition of Grignard reagents to α,β-unsaturated esters with Cu-ferrocenylphosphines[8] or Cu-2,2′-bis(di-p-tolylphosphino)-1,1′-binaphthalene (CuTolyl-BINAP)[9] complexes. In the first case, good yields and enantiomeric excesses were obtained with several Grignard reagents but not with methylmagnesium bromide, which instead gave good conversions and excellent enantioselectivities when Tolyl-BINAP was used as ligand. These results are particularly interesting due to the remarkable importance of chiral 3-alkylsubstituted esters, as well as corresponding alcohols and acids, both in asymmetric synthesis and as precursors of biologically active compounds. Although several Grignard reagents are commercially available and inexpensive, dialkylzinc reagents offer however some advantages because of their better tolerance toward several functional groups.[10] An indirect method to obtain optically active 3-methylesters by copper-catalyzed conjugate addition of diorganozinc reagents was developed by Feringa and coworkers,[11] who reported an efficient asymmetric addition of dimethylzinc to alkylidenmalonates in the presence of phosphoramidite ligands. The addition products in fact can be easily transformed in 3-alkyl substituted monoesters by direct dealkoxycarbonylation.[12]

We decided to explore, herein, the behavior of a variety of phosphorous ligands in the copper-catalyzed asymmetric addition of dimethylzinc to 3-phenylpropylidenmalonate with the aim to disclose new synthetic applications of this procedure. In fact, the asymmetric conjugate addition of dimethylzinc to unsaturated compounds can be a very direct method to obtain a methyl-substituted stereogenic center, a structural motif that often plays an important role in determining the biological activity of numerous natural compounds. In particular, we focused our attention on the development of new synthetic approaches for the preparation in optically active form of some valuable fragrances such as 3-methyl-5-phenyl-pentanol (Phenoxanol) and the structurally related fragrances 3-methyl-5-phenyl-pentanaldehyde (Citralis) and 3-methyl-5-phenyl-pentanenitrile (Nitrile Citralis)[13,14] (Scheme 1), choosing 3-phenylpropylidenmalonate (**5**) as starting substrate on which to test the asymmetric addition.

These three synthetic fragrances posses floral and fruity notes (rose, lily-of-the-valley, citrus) and are commercially available in racemic form. An efficient asymmetric synthesis of Phenoxanol, as well as its transformation in Citralis and Nitrile Citralis, was reported by Matteoli[14] who also reported the odor profiles of the single enantiomers, showing a significant difference in odor threshold between compounds with opposite configuration and, for Phenoxanol, also in olfactorily notes. Such a synthetic procedure was based on the asymmetric hydrogenation of (*Z*)- or (*E*)-allylic alcohols with Ru-2,2′-bis(diphenylphosphino)-1,1′-binaphtalene (BINAP) complexes giving products in high enantiomeric excesses, but requiring high hydrogen pressure (100 atm) and long reaction times (48 h) for the complete conversion. On the other hand, we propose, herein, a new and mild access to Phenoxanol based on the asymmetric addition of dimethylzinc to 3-phenylpropylidenmalonate, in turn easily achievable by Knoevenagel reaction from inexpensive chemicals, followed by deethoxycarbonilation and reduction of the optically active ester.

Contract grant sponsors: MIUR-PRIN 2008LYSEBR and Università della Basilicata (Potenza).
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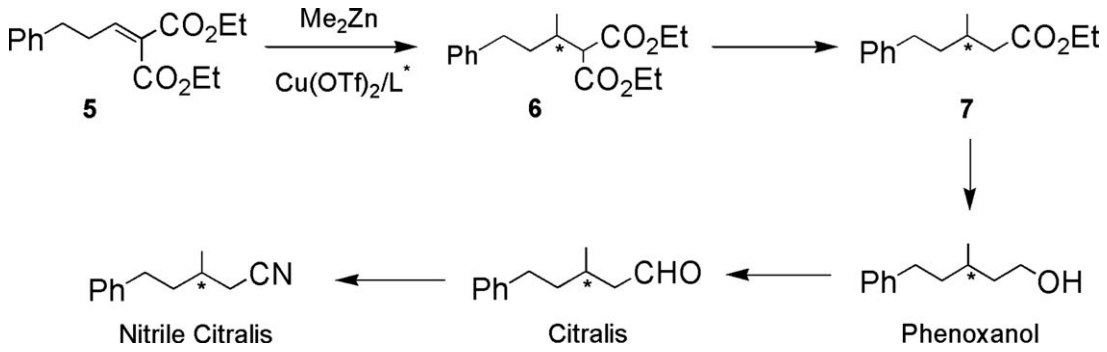
Received for publication 10 May 2011; accepted in revised form 12 May 2011; Accepted 17 May 2011
DOI: 10.1002/chir.20987
Published online 17 August 2011 in Wiley Online Library (wileyonlinelibrary.com).



Scheme 1. Synthetic scheme to Phenoxanol, Citralis, and Nitrile Citralis.

EXPERIMENTAL

General Procedures

^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded in $CDCl_3$ on a Varian INOVA 400 spectrometer, using tetramethylsilane (TMS) as an internal standard. ^{31}P (162 MHz) NMR spectra were recorded in $CDCl_3$ on a Varian INOVA 400 spectrometer, using triphenylphosphate ($CDCl_3$, −17.7 ppm) as an external standard. GC–MS spectra were recorded on a Hewlett Packard 6890 gas chromatograph, equipped with a mass spectrometric detector HP-5973 type and a capillary column HP-5MS 30 m × 0.25 mm. Melting points were taken using a Kofler Reichert-Jung thermovar apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. HPLC analyses were performed on a JASCO PU-1580 intelligent HPLC pump equipped with a Varian 2550 UV detector and CHIRALCEL OJ-H column. Thin layer chromatography (TLC) analyses were performed on silica gel 60 Macherey-Nagel sheets, flash chromatography separations were carried out using silica gel 60 (70–230 mesh). Toluene was distilled over sodium-benzophenone, whereas dichloromethane and chloroform were distilled over calcium hydride prior their use. DIBALH (Aldrich) was a 1.5 M solution in toluene, Me_2Zn (Aldrich) was a 2 M solution in toluene, MeMgBr (Aldrich) was a 3 M solution in Et_2O. PCl_3 was distilled, under nitrogen, before its use. Et_3N was distilled over calcium hydride, under nitrogen, before its use. *N,N*-Dimethylaminopyridine (DMAP) and (*R*)- and (*S*)-1,1'-bi(2-naphtol) (BINOL) were dried heating at 50°C at reduced pressure, for 5 h, before the use. Preparation of (*S*)-**L1**,[15,16] (*aR,R,R*)-**L2a**,[17] (*aS,R,R*)-**L3a**,[17] (*R,R*)-**9a**,[18] (*R,R*)-**10a**,[18] (*R,R*)-**9d**,[19] and (*R,R*)-**10d**[19] has been described elsewhere. Diethyl 3-phenylpropylidenemalonate (**5**) was prepared in 43% yield according to literature procedure[11] starting from 3-phenylpropionaldehyde. Enantiopure (*R,R*)-1,2-diphenylethane-1,2-diol (**8a**)[20] and (*R,R*)-1,2-di(2-naphthyl)-ethane-1,2-diol (**8b**)[21] were prepared according to literature procedures.

Synthesis of (4R,5R)-2-aryl-4,5-diphenyl-1,3-dioxolanes 9b-c,e. A solution of arylaldehyde (2.81 mmol), (*R,R*)-**8a** or (*R,R*)-**8b** (2.34 mmol) and traces of *p*-toluensulfonic acid in toluene (30 ml) was heated at reflux under Dean-Stark conditions. The reaction was monitored by GC–MS analysis. After complete conversion, the solvent was removed at reduced pressure, and the residue was purified by column chromatography (SiO_2, $CHCl_3$, or $CHCl_3$/petroleum ether).

(4R,5R)-2-(Naphthalen-1-yl)-4,5-diphenyl-1,3-dioxolane (9b). Yield 78% (white solid); m.p. = 83–86°C; $[\alpha]^{20}_D$ = −13.3 (c 1.01, $CHCl_3$); MS (EI): *m/z* 246 (M^+ − PhCHO, 100), 217 (58), 167 (12), 155 (24), 139 (28), 127 (15); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.05 (d, *J* = 8.0 Hz, 1H), 5.14 (d, *J* = 8.0 Hz, 1H), 7.09 (s, 1H), 7.37–7.43 (m, 10H), 7.55–7.61 (m, 3H), 7.94 (d, *J* = 8.0 Hz, 2H), 8.05 (d, 7.2 Hz,1H), 8.40 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 85.41, 87.54, 103.19, 123.82, 124.39, 125.39, 126.02, 126.66, 126.73, 127.23, 128.51, 128.77, 128.83, 129.96, 131.29, 133.55, 134.08, 136.76, 138.43.

(4R,5R)-2-(Naphthalen-2-yl)-4,5-diphenyl-1,3-dioxolane (9c). Yield 66% (white solid); m.p. = 82–85°C; $[\alpha]^{20}_D$ = −1.4 (c 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 5.00 (d, *J* = 8.1 Hz, 1H), 5.03 (d, *J* = 8.1 Hz, 1H), 6.59 (s, 1H), 7.3−7.5 (m, 10H), 7.51 (t, *J* = 3.1 Hz, 1H), 7.54 (t, *J* = 3.1 Hz, 1H), 7.8 (dd, J_1 = 8.4 Hz, J_2 = 1.4 Hz, 1H), 7.9−8.0 (m, 3H), 8.12 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 86.44, 86.91, 107.00, 125.32, 126.74, 127.07, 127.32, 127.63, 127.81, 128.54, 131.00, 133.00, 135.03, 136.41.

(4R,5R)-4,5-Di(naphthalen-2-yl)-2-phenyl-1,3-dioxolane (9e). Yield 86% (pale yellow solid); m.p. = 112–115°C; $[\alpha]^{20}_D$ = +65.2 (c 1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.25 (s, 2H), 6.58 (s, 1H), 7.44–7.58 (m, 8H), 7.76–7.78 (m, 6H), 7.87–7.92 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 85.67, 87.63, 105.17, 124.35, 124.58, 125.86, 126.54, 127.02, 127.99, 128.32, 128.80, 129.73, 133.54, 133.72, 134.15, 135.83, 138.42.

Synthesis of monobenzylethers 10b-c, e. To a solution of the dioxolane **9b,c,e (**1.82 mmol) in toluene (10 ml), under nitrogen, a solution of DIBALH (6.64 mmol) was slowly added at 0°C. The reaction was monitored by GC–MS analysis. The reaction was quenched with a few drops of methanol, then the solution was diluted with diethyl ether, washed with 10% aqueous NaOH, brine and dried over Na_2SO_4. After the evaporation of the solvent, the residue was purified by chromatography column (SiO_2, petroleum ether/Et_2O 3:1).

(1R,2R)-2-(Naphthalen-1-yl-methoxy)-1,2-diphenylethanol (10b). Yield 82% (white solid); m.p. = 70–72°C; $[\alpha]^{20}_D$ = −41.8 (c 1.08, $CHCl_3$); MS (EI): *m/z* 141 (M^+ − $C_{14}H_{13}O_2$, 100), 107 (32), 79 (11); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.34 (bs, 1H), 4.35 (d, *J* = 8.0 Hz, 1H), 4.68 (d, *J* = 11.6 Hz, 1H), 4.90 (d, *J* = 11.6 Hz, 1H), 6.92–6.94 (m, 2H), 7.04–7.08 (m, 5H), 7.16–7.20 (m, 3H), 7.33–7.37 (m, 2H), 7.41–7.48 (m, 2H), 7.76 (dd, J_1 = 6.8 Hz, J_2 = 2.0 Hz, 1H), 7.80 (d, *J* = 7.2 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 69.47, 78.72, 87.39, 123.92, 125.41, 126.08, 126.66, 127.12, 127.44, 127.84, 128.00, 128.16, 128.40, 128.90, 129.14, 132.00, 134.00, 137.76, 139.32.

(1R,2R)-2-(Naphthalen-2-yl-methoxy)-1,2-diphenylethanol (10c). Yield 76% (white solid); m.p. = 91–93°C; $[\alpha]^{20}_D$ = −28.0 (c 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.56 (s, 1H), 4.41 (d, *J* = 8.2 Hz, 1H), 4.49 (d, *J* = 11.6 Hz, 1H), 4.70 (d, *J* = 11.6 Hz, 1H), 4.77 (d, *J* = 8.2 Hz, 1H), 7.00–7.30 (m, 4H), 7.40–7.50 (m, 5H), 7.73 (s, 1H), 7.8–7.9 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 72.89, 77.65, 90.35, 125.43, 126.32, 127.51, 127.82, 128.65, 128.92, 131.65, 133.82, 135.25, 136.90, 138.43.

(1R,2R)-2-(Benzyloxy)-1,2-di(naphthalen-2-yl)ethanol (10e). Yield 64% (yellow pale oil); $[\alpha]^{20}_D$ = +103.6 (c 0.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.63 (bs, 1H), 4.30 (d, *J* = 11.2 Hz, 1H), 4.47 (d, *J* = 11.2 Hz, 1H), 4.55 (d, *J* = 8.0 Hz, 1H), 4.95 (d, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.22–7.37 (m, 7H), 7.48–7.64 (m, 6H), 7.71 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 71.15, 78.69, 87.03, 125.49, 125.55, 125.63, 126.02, 126.35, 126.60, 127.69, 127.79, 127.94, 128.19, 128.22, 128.28, 128.34, 128.48, 128.78, 129.29, 133.24, 133.27, 133.29, 133.52, 135.28, 136.96, 137.88.

Synthesis of (4R,5R)-4,5-diphenyl-3′,4′-dihydro-2′H-spiro[[1,3] dioxolane-2,1′-naphthalene] (12). To a solution of α-tetralone

(0.45 ml, 3.42 mmol) in methanol (7.5 ml), trimethyl orthoformate (0.75 ml, 6.84 mmol) and traces of *p*-toluensulfonic acid were added. The red–orange solution was stirred at room temperature for 6 h monitoring the reaction by GC–MS analysis. Then the reaction mixture was diluted with diethyl ether and treated with aqueous 1 M NaOH. The aqueous phase was extracted with diethyl ether and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated at reduced pressure to give 1,1-dimethoxy-1,2,3,4-tetrahydronaphthalene (0.60 g, 3.10 mmol, which was dissolved in chloroform (39 ml). To this solution, (*R*,*R*)-**8a** (0.64 g, 3.00 mmol), activated molecular sieves (4 Å), traces of *p*-toluensulfonic acid were added, and the mixture was stirred at room temperature for 20 h. The reaction was monitored by GC–MS analysis. Filtration and evaporation of solvent at reduced pressure gave the crude product, which was purified by chromatography column (SiO_2, petroleum ether/dichloromethane 6:4) to provide **12** (0.69 g, 67%) as white solid.

M.p. = 109–111°C; $[\alpha]^{20}_D = +69.9$ (c 1.02, $CHCl_3$); MS (EI): *m/z* 236 (M^+ − PhCHO, 100), 218 (13), 208 (12), 180 (29), 167 (16), 129 (24), 118 (21), 91 (14); ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 2.02 (q, *J* = 6.0 Hz, 2H), 2.25 (t, *J* = 6.0 Hz, 2H), 2.79 (t, *J* = 6.4 Hz, 2H), 4.85 (d, *J* = 8.4 Hz, 1H), 5.01 (d, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 7.2 Hz, 1H), 7.14–7.25 (m, 12H), 7.77 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 21.10, 29.35, 35.68, 85.43, 86.92, 108.20, 126.61, 126.72, 126.82, 127.26, 127.28, 128.38, 128.65, 128.78, 128.91, 136.38, 137.84, 138.14, 138.80.

Synthesis of (1R,2R)-1,2-diphenyl-2-(1,2,3,4-tetrahydronaphthalen-1-yloxy)ethanol (13). To a solution of **12** (0.63 g, 1.85 mmol) in dichloromethane (10 ml), a solution of DIBALH (7.4 ml, 6 eq., 11.10 mmol) was slowly added at 0°C. The reaction was monitored by GC–MS analysis. The reaction was quenched with a few drops of methanol, then diluted with diethyl ether, washed with 10% aqueous NaOH, brine, and dried over Na_2SO_4. The evaporation of solvent gave the product **13** (0.58 g, 91%) as colorless oil.

$[\alpha]^{20}_D = -79.8$ (c 1.17, $CHCl_3$); MS (EI): *m/z* 131 ($M^+ - C_{14}H_{13}O_2$, 100), 213 (15), 107 (78), 91 (19), 79 (16); ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 1.18–1.57 (m, 2H), 1.76–1.82 (m, 1H), 1.90–1.96 (m, 1H), 2.56–2.64 (m, 1H), 2.77 (dt, J_1 = 16.4 Hz, J_2 = 5.2 Hz, 1H), 3.35 (s, 1H), 4.39–4.42 (m, 2H), 4.57 (d, *J* = 8.0 Hz, 1H), 6.90–6.93 (m, 2H), 7.01–7.19 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 18.26, 28.89, 29.78, 75.41, 79.12, 86.94, 125.90, 127.50, 127.80, 128.10, 128.20, 128.30, 129.70. 136.30, 138.10, 139.30, 139.50.

Synthesis of phosphites (aR,R,R)-L2a-e, (aS,R,R)-L3a, (aS,R,R)-L3e and (aR,R,R)-L4. A solution of monoprotected diarylethane-1,2-diols **10a–e** or **13** (1.96 mmol) in toluene (6 ml) was slowly added to a cooled solution (–60°C) of freshly distilled phosphorus trichloride (171 μl, 1.96 mmol) and triethylamine (1.4 ml, 10.24 mmol) in toluene (4 ml). The mixture was stirred at −60°C for 2 h. Then DMAP (261 mg, 2.14 mmol) was added to the solution, and a solution of (*R*) or (*S*)-BINOL (561 mg, 1.96 mmol) was added dropwise in toluene (16 ml). The solution was stirred at −60°C for 2 h. The reaction was monitored by TLC. The reaction mixture was filtered and concentrated at reduced pressure. The purification of the crude product, by chromatography column (SiO_2, dichloromethane/petroleum ether 2:1), gave the phosphite as white solid.

(aR,R,R)-L2a. Yield (55%); m.p. = 107–109°C; $[\alpha]^{20}_D = -246.0$ (c 0.55, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 4.48 (d, *J* = 11.7 Hz, 1H), 4.49 (d, *J* = 8.1 Hz), 4.53 (d, *J* = 11.7 Hz, 1H), 5.42 (dd, J_1 = 8.7 Hz, J_2 = 8.1 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 1H), 6.93 (d, *J* = 7.2 Hz, 2H), 7.06 (d, *J* = 6.4 Hz, 2H), 7.1–7.4 (m, 18 H), 7.72 (d, *J* = 9.0 Hz, 1H), 7.8–7.9 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 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)-L3a. Yield (20%); m.p. = 97–100°C; $[\alpha]^{20}_D = +221.0$ (c 0.53, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 4.50 (d, *J* = 11.7 Hz, 1H), 4.56 (d, *J* = 11.7 Hz, 1H), 4.64 (d, *J* = 7.5 Hz, 1H), 5.43 (dd, J_1 = 7.8 Hz, J_2 = 7.5 Hz, 1H), 6.90 (d, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 2H), 7.1–7.5 (m, 20H), 7.69 (d, *J* = 9.0 Hz, 1H), 7.90–8.00 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 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.

(aR,R,R)-L2b. Yield (22%); m.p. = 152–155°C; $[\alpha]^{20}_D = -176.1$ (c 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 4.63 (d, *J* =8.0 Hz, 1H), 4.94 (s, 2H), 5.44 (dd, J_1 = 9.6 Hz, J_2 = 8.0 Hz, 1H), 6.73 (d, *J* = 8.8 Hz, 1H), 6.97 (t, *J* = 7.2 Hz, 2H), 7.11 (d, *J* = 10.0 Hz, 2H), 7.14–7.27 (m, 10H), 7.31–7.52 (m, 6H), 7.66–7.69 (m, 2H), 7.77–7.89 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$), δ (ppm): 66.52, 89.45, 103.42, 122.71, 124.22, 125.86, 126.11, 126.36, 127.28, 127.90, 127.97, 128.20, 128.34, 128.45, 128.63, 131.35, 131.61, 133.76, 137.49, 139.61, 167.14, 167.82.

(aR,R,R)-L2c. Yield (35%); m.p. = 173–176°C; $[\alpha]^{20}_D = -184.5$ (c 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 4.46 (d, *J* = 8.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 5.38 (dd, J_1 = 9.2 Hz, J_2 = 8.4 Hz, 1H), 6.74 (d, *J* = 8.8 Hz, 1H), 6.89 (d, *J* = 7.2 Hz, 2H), 6.97–7.01 (m, 2H), 7.07–7.21 (m, 10 H), 7.29–7.46 (m, 6H), 7.64–7.83 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 71.20, 86.05, 107.91, 122.21, 122.80, 123.26, 125.16, 125.55, 126.15, 126.23, 126.33, 127.27, 127.89, 127.99, 128.30, 128.40, 128.49, 129.29, 130.27, 131.39, 131.68, 132.82, 133.02, 133.16, 133.57, 136.11, 137.48, 167.75.

(aR,R,R)-L2d. Yield (14%); m.p. = 108–110°C; $[\alpha]^{20}_D = -26.3$ (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 4.52 (d, *J* = 10.0 Hz, 1H), 4.57 (d, *J* = 10.0 Hz, 1H), 4.75 (d, *J* = 8.0 Hz, 1H), 5.44 (t, *J* = 8.8 Hz, 1H), 6.64 (d, *J* = 7.2 Hz, 1H), 6.70 (d, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 8.8 Hz, 1H), 6.95–7.65 (m, 20H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.80–7.97 (m, 6H), 8.04 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 75.83, 91.47,73.94, 119.00, 124.41, 126.63, 126.91, 127.68, 127.89, 127.99, 128.00, 128.61, 128.89, 129.20, 129.48, 130.77, 133.87, 137.41, 141.87, 153.00.

(aR,R,R)-L2e. Yield (32%); m.p. = 126–129°C; $[\alpha]^{20}_D = -153.2$ (c 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 1.46–1.57 (m, 2H), 1.69–1.74 (m, 1H), 1.88–1.93 (m, 1H), 2.58 (dt, J_1 = 16.8 Hz, J_2 = 6.8 Hz, 1H), 2.76 (dt, J_1 = 16.8 Hz, J_2 = 6.0 Hz, 1H), 4.49 (t, *J* = 4.6 Hz, 1H), 4.58 (d, *J* = 7.6 Hz, 1H), 5.27 (dd, J_1 = 10.4 Hz, J_2 = 8.0 Hz, 1H), 6.39 (d, *J* = 8.8 Hz, 1H), 6.87 (d, *J* = 7.2 Hz, 2H), 6.97–7.37 (m, 18H), 7.43 (d, *J* = 8.8 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7,77 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 18.51, 28.91, 29.59, 76.00, 84.57, 87.91, 115.71, 122.06, 122.59, 123.05, 124.90, 125.18, 125.56, 126.10, 126.37, 127.22, 127.93, 128.11, 128.30, 129.20, 129.45, 130.41, 131.31, 132.71, 134.13, 136.70, 138.00, 138.19, 139.32, 148.23; ^{31}P NMR (162 MHz, $CDCl_3$), δ (ppm):152.22.

(aS,R,R)-L3e. Yield (52%); m.p. = 137–139°C; $[\alpha]^{20}_D = +205.7$ (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 1.43–1.55 (m, 2H), 1.90–1.92 (m, 1H), 2.12–2.14 (m, 1H), 2.54–2.65 (m, 1H), 2.72–2.76 (m, 1H), 4.30–4.33 (m, 1H), 4.66 (d, *J* = 6.8 Hz, 1H), 5.23 (dd, J_1 = 8.8 Hz, J_2 = 6.8 Hz, 1H), 6.16 (d, *J* = 8.4 Hz, 1H), 6.65 (d, *J* = 7.2 Hz, 2H), 6.92–7.34 (m, 18H), 7.46 (d, *J* = 8.8 Hz, 1H), 7.76–7.88 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 17.99, 29.74, 35.17, 73.39, 86.97, 96.39, 124.80, 125.21, 125.51, 125.97, 126.26, 127.35, 127.64, 127.69, 127.90, 128.15, 128.37, 128.42, 129.45, 129.91, 130.26, 132.58, 133.04, 138.50, 138.72, 139.31, 139.91, 150.42, 157.40; ^{31}P NMR (162 MHz, $CDCl_3$), δ (ppm):144.33.

(aR,R,R)-L4. Yield (50%); m.p. = 165–168°C; $[\alpha]^{20}_D = -93.3$ (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 4.43 (d, *J* =11.2 Hz, 1H), 4.48 (d, *J* =12.0 Hz, 1H), 4.67 (d, *J* =7.6 Hz, 1H), 5.64 (dd, J_1 = 9.2 Hz, J_2 = 8.0 Hz, 1H), 6.66 (d, *J* =8.8 Hz, 1H), 6.88 (d, *J* =7.2 Hz, 1H), 7.05–7.41 (m, 20H), 7.47–7.59 (m, 5H), 7.69 (d, *J* =6.8 Hz, 2H), 7.80–7.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 71.25, 81.20, 86.09, 122.12, 122.84, 123.31, 125.17, 125.69, 125.83, 126.32, 127.28, 127.48, 127.86, 128.29, 128.51, 130.32, 130.80, 131.43, 131.71, 132.86, 133.10, 133.24, 133.27, 133.48, 134.94, 135.31, 138.51, 145.61, 148.07, 148.34, 156.31.

Synthesis of racemic 3-methyl-5-phenylpentanoate (7). To a mixture of MeMgBr (800 μl, 2.30 mmol) and CuCl (80 mg, 0.78 mmol) in Et_2O (2.3 ml), a solution of diethyl 3-phenylpropylidenemalonate (**5**) (160 mg, 0.58 mmol) in Et_2O (2.3 ml) was added, and the mixture was stirred at room temperature for 2 h. The reaction was monitored by GC–MS analysis. The reaction was quenched with 10% aqueous HCl, and the solution extracted with Et_2O. The organic phases were washed with brine, dried over anhydrous Na_2SO_4. The evaporation of solvent at reduced pressure gave diethyl 2-(4-phenylbutan-2-yl)malonate (**6**) (91 mg, 0.31 mmol) which was dissolved in DMF (1.1 ml). To this solution, H_2O (11 μl, 0.62 mmol) and LiCl (53 mg, 1.24 mmol) were added, and the reaction mixture was heated to reflux for 20 h. After cooling at room temperature, water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. The evaporation of solvent at reduced pressure gave the crude product, which was purified by chromatography column (SiO_2, petroleum ether/CH_2Cl_2 8:2) to provide ethyl 3-methyl-5-phenylpentanoate (**7**) (34 mg, 50%) as pale yellow oil. The two enantiomers were separated by HPLC on Chiralcel OJ-H column, 210 nm, 0.5 ml/min, hexane/2-propanol 90/10. MS (EI): *m/z* 220 (M^+, 3), 174 (79), 131 (32), 104 (24), 91 (100); ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 0.93 (d, J = 6.4 Hz, 3H), 1.17 (t, J = 7.2 Hz, 3H), 1.40–1.50 (m, 1H), 1.53–1.62 (m, 1H), 1.91–2.00 (m, 1H), 2.05–2.12 (m, 1H), 2.28 (dd, J_1 = 15.6 Hz, J_2 = 6.0 Hz, 1H), 2.52–2.62 (m, 2H), 4.04 (q, J = 7.2 Hz, 2H), 7.10–7.21 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 14.48, 19.88, 29.94, 33.57, 38.78, 42.05, 49.91, 60.41, 124.40, 128.59, 131.60, 136.80, 168.38.

General Procedure

Enantioselective Addition of Me_2Zn to diethyl 3-phenylpropylidenemalonate (5). A solution of flamed dried $Cu(OTf)_2$ (8.1 mg, 0.022 mmol, 4 mol %) and phosphoramidite or phosphite ligand (0.045 mmol, 8 mol %) in freshly distilled toluene (4 ml) was stirred at room temperature for 1 h. After cooling to −40°C, diethyl 2-(3-phenylpropylidene)malonate (**5**) (155 mg, 0.56 mmol) and Me_2Zn (0.7 ml, 2 eq., 1.12 mmol) were slowly added. The reaction was monitored by GC–MS analysis. After complete conversion, the mixture was poured into a solution of saturated NH_4Cl and ethyl acetate. The separated organic layer was washed with brine and dried over Na_2SO_4. The evaporation of solvent at reduced pressure gave the diethyl 2-(4-phenylbutan-2-yl)malonate (**6**) (159 mg, 97%). This compound was deethoxycarbonylated to **7** according to the procedure reported above for the racemic mixture. Enantiomeric excesses were determined by HPLC, in the same conditions reported above.

Synthesis of 3-methyl-5-phenylpentan-1-ol (Phenoxanol). Under nitrogen atmosphere, to a solution of (*R*)-ethyl-3-methyl-5-phenylpentanoate (**7**) (74% ee) (124 mg, 0.56 mmol) in Et_2O (2.8 ml), at 0°C, DIBALH (1.12 ml, 3 eq., 1.68 mmol) was slowly added. The reaction mixture was stirred, at the same temperature, for 16 h. The solution was diluted with Et_2O and quenched with brine. Then HCl 4 M was added dropwise under stirring until two clear and separated phases were formed. The aqueous layer was extracted with Et_2O, and the combined organic phases were washed with brine and dried over Na_2SO_4. The evaporation of solvent at reduced pressure gave (*R*)-Phenoxanol (93 mg, 93%). $[\alpha]^{20}_D$ = +11.0 (c 3.00, CH_2Cl_2) (74% ee); MS (EI): *m/z* 178 (M^+, 3), 160 (49), 145 (8), 131 (33), 117 (30), 104 (85), 92 (53), 91 (100); ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 0.99 (d, J = 6.5 Hz, 3H), 1.45–1.52 (m, 2H), 1.64–1.71 (m, 3H), 2.60–2.76 (m, 2H), 3.43 (d, J = 6.5 Hz, 1H), 3.68–3.76 (m, 2H), 7.18–7.21 (m, 3H), 7.28–7.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 19.79, 29.50, 33.62, 39.26, 40.05, 61.33, 125.89, 128.57, 129.28, 143.06.

Synthesis of 3-methyl-5-phenylpentanal (Citralis). To a solution of pyridinium chlorochromate (224 mg, 1.04 mmol) in CH_2Cl_2 (1.8 ml), 3-methyl-5-phenylpentan-1-ol (93 mg, 0.52 mmol) in CH_2Cl_2 (0.2 ml) was added, and the solution was stirred at room temperature for 1 h. The reaction was monitored by GC–MS. After removal of the solvent, the residue was diluted with Et_2O and filtered through a short plug of silica gel to afford (*R*)-Citralis (65 mg, 71%), which was utilized in the next step without purification. $[\alpha]^{20}_D$ = +17.4 (c 1.0, CH_2Cl_2) (74% ee); MS (EI): *m/z* 176 (M^+, 31), 158 (13), 143 (36), 131 (22), 117 (42), 105 (20), 92 (36), 91 (100), 71 (24); ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 1.03 (d, J = 7.0 Hz, 3H), 1.64–1.70 (m, 2H), 2.09–2.13 (m, 1H), 2.28 (ddd, J_1 = 16.0 Hz, J_2 = 7.5 Hz, J_3 =2.5 Hz, 1H), 2.44 (dd, J_1 = 16.0 Hz, J_2 = 4.0 Hz, 1H), 2.57–2.71 (m, 2H), 7.17–7.20 (m, 2H), 7.26–7.29 (m, 3H), 9.75 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 19.79, 27.80, 33.16, 38.58, 50.90, 125.80, 128.29, 128.40, 142.03, 202.68.

Synthesis of 3-methyl-5-phenylpentanenitrile (Nitrile Citralis). To a solution of $NH_2OH{\cdot}HCl$ (34 mg, 0.48 mmol), NaI (28 mg, 0.18 mmol) in MeCN (1.5 ml) was added a solution of 3-methyl-5-phenylpentanal (65 mg, 0.37 mmol) in MeCN (2 ml), and the reaction mixture was heated at reflux for 1 h. The reaction was monitored by GC–MS. The red mixture was cooled to room temperature, quenched with 5% aqueous $Na_2S_2O_3$ and stirred until complete disappearance of the red color. The solution was diluted with CH_2Cl_2, the organic layer was washed with brine and dried over Na_2SO_4. The evaporation of solvent at reduced pressure gave the (*R*)-Nitrile Citralis (53 mg, 83%). $[\alpha]^{20}_D$ = −1.7 (c 3.0, CH_2Cl_2) (74% ee); MS (EI): *m/z* 173 (M^+, 20), 158 (43), 92 (29), 91 (100); ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 1.06 (d, J = 6.8 Hz, 3H), 1.59–1.69 (m, 2H), 1.80–1.90 (m, 1H), 2.51–2.64 (m, 4H), 7.06–7.25 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 19.29, 24.50, 29.87, 33.00, 37.48, 118.68, 126.00, 128.16, 128.50, 141.28.

RESULTS AND DISCUSSION

At first, phosphoramidite (*S*)-**L1**[15,16] and phosphites (*aR,R,R*)-**L2a** and (*aS,R,R*)-**L3a**[17] (Chart 1) which proved to efficiently catalyze the asymmetric addition of dimethylzinc to macrocyclic enones, were tested as ligands in the copper-catalyzed asymmetric addition of dimethylzinc to diethyl 3-phenylpropylidenmalonate (**5**) (Table 1), screening various temperatures to find the best experimental conditions for the two ligands. Performing the reaction at −60°C phosphoramidite (*S*)-**L1** provided very poor stereoselection (10% ee) after 30 h (Entry 1), while increasing the temperature better yields and enantiomeric excesses (Entries 2–4) were obtained, arriving up to 66% ee at 0°C (Entry 4). On the contrary, (*aR,R,R*)-**L2a** provided the highest yield and e.e (72%) at −40°C (Entry 6). The diastereoisomeric phosphite

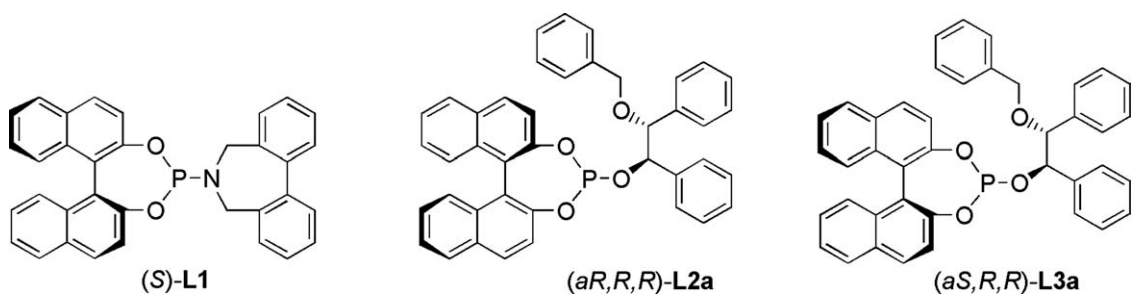
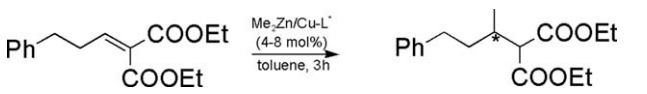


Chart 1. Structures of ligands **L1**, **L2a**, **L3a**.

TABLE 1. Asymmetric addition of Me_2Zn to diethyl 3-phenylpropylidenmalonate (5) with L1, L2a, and L3a



Entries	Ligand	T (°C)	Yield (%)[a]	ee (%)[b] A.C.[c]
1[d]	(*S*)-**L1**	−60	79	10 (*S*)
2	(*S*)-**L1**	−40	96	50 (*S*)
3	(*S*)-**L1**	−20	95	44 (*S*)
4	(*S*)-**L1**	0	87	66 (*S*)
5	(*aR,R,R*)-**L2a**	−60	70	64 (*R*)
6	(*aR,R,R*)-**L2a**	−40	93	72 (*R*)
7	(*aR,R,R*)-**L2a**	−20	91	48 (*R*)
8	(*aR,R,R*)-**L2a**	0	61	48 (*R*)
9	(*aS,R,R*)-**L3a**	−40	54	18 (*S*)

[a]Isolated yield.
[b]Determined by chiral HPLC analysis of the corresponding monoester **7**.
[c]Determined from sign of optical rotation of the corresponding monoester **7** (see Ref. 11).
[d]Complete conversion after 30 h.

(*aS,R,R*)-**L3a**, in which the binaphthyl moiety have opposite configuration, provided (Entry 9) a reversed enantioselectivity and significantly lower ee (18%) in respect to (*aR,R,R*)-**L2a**. We can then deduce that in this reaction, although the effect of the binaphthyl backbone is predominant in determining the direction of the asymmetric induction, also the fragment derived from monoprotected diphenylethane-1,2-diol plays an important role in the efficiency of phosphites as chiral ligands. This is clear from the difference of ees values achieved with the two diastereoisomer ligands.

Taking into account the aforementioned considerations as well as the fact that, in this reaction, phosphite (*aR,R,R*)-**L2a** provided the best results, we decided to modify the structure of this easily tunable ligand to try to improve the enantioselectivity. To this end, several new phosphites derived from BINOL but displaying different alcoholic moieties were synthesized (Chart 2). A summary of the synthetic steps for their preparation is reported in the Scheme 2.

We first synthesized and tested ligands (*aR,R,R*)-**L2b-d**, which share a different monoprotection of the alcohol part deriving from the diol.[18] (*R,R*)-1,2-diphenylethane-1,2-diol (**8a**)[20] and (*R,R*)-1,2-di(2-naphthyl)ethane-1,2-diol (**8b**)[21] were obtained by asymmetric dihydroxylation of the corresponding alkenes. Acetals **9a–e** were prepared in 80–90% yield by reacting (*R,R*)-**8a,b** with a suitable arylaldehyde and a catalytic amount of *p*-TsOH, in refluxing benzene under water removal using a Dean-Stark condenser.[18,19] The monobenzylethers **10a–e** were obtained in 70–90% yield by reduction of the acetals **9a–e** with a threefold excess of DIBALH in dry toluene at 0°C.[18,19] Monoprotected diols **10a–e** were then transformed in the corresponding dichlorophosphites **11a–e** by treatment with phosphorus trichloride and triethylamine in toluene. Further treatment of **11a–e** with (*R*) or (*S*)-BINOL at −60°C in toluene in the presence of DMAP provided the desired phosphites **L2a-d** and **L4**. These phosphites were then screened using the experimental conditions optimized for (*aR,R,R*)-**L2a** (Table 2) obtaining enantioselectivity (ee 62–74%) comparable with that achieved with this ligand (Table 2, Entries 1–3).

We thought then that a reduction of the conformational freedom of the benzylic protecting group of the alcoholic function could have a positive effect on the efficiency of the ligand. Therefore, we projected a phosphite in which the benzylic carbon linked to the oxygen of the diol was inserted in a cycle, then limiting its conformational flexibility. Therefore, starting from tetralone acetal **12** was prepared with diol (*R,R*)-**8a** (Scheme 3). The acetal was then opened into the corresponding monoprotected diol **13** by treatment with DIBALH. From both ^{1}H NMR and ^{13}C NMR analyses of crude, a single set of signals allied to a single diastereoisomer of **13** was detected (see Experimental Section), in agreement with results previously reported by Sharpless.[20]

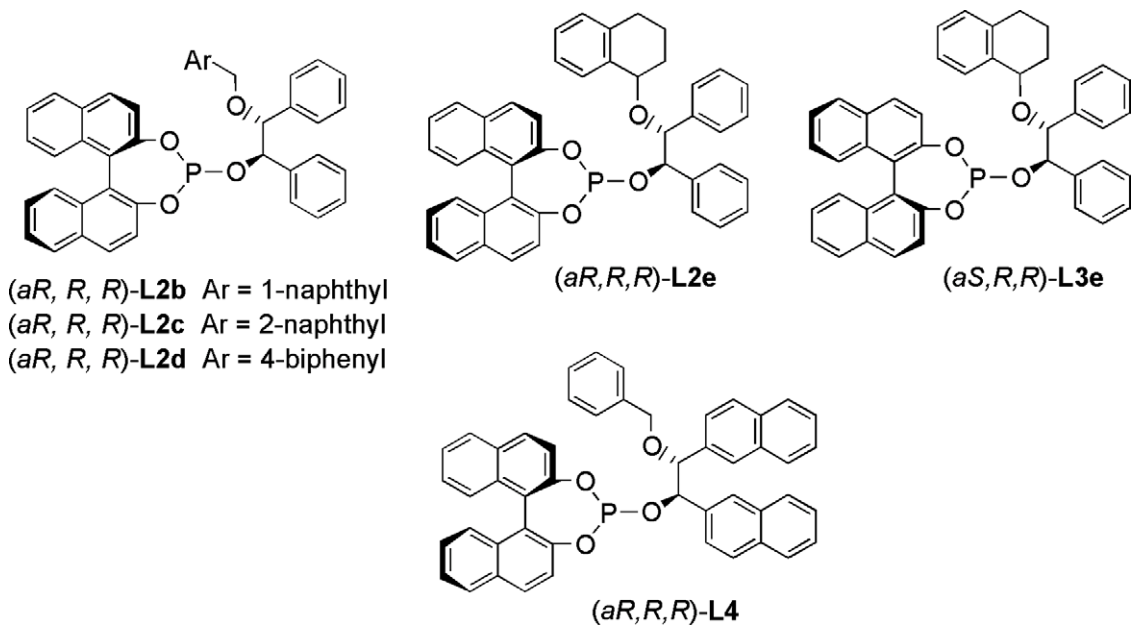
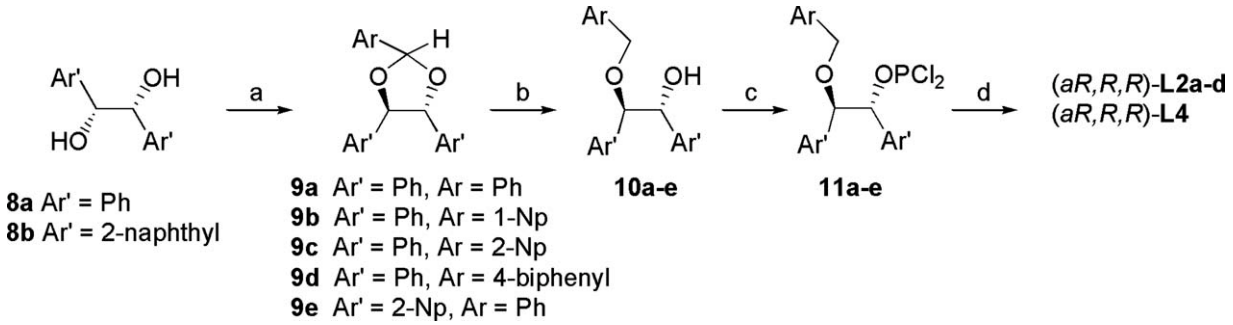
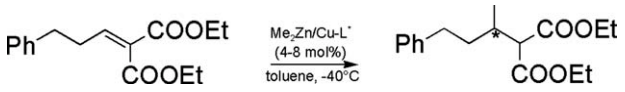


Chart 2. Structures of new phosphites.



Scheme 2. Reagent and conditions: (**a**) ArCHO, *p*-TsOH, toluene, Dean-Stark; (**b**) DIBAL, toluene, 0°C; (**c**) PCl_3, Et_3N, toluene, −60°C; (**d**) DMAP, (*R*) or (*S*)-BINOL, toluene, −60°C.

TABLE 2. Asymmetric addition of Me_2Zn to diethylpropylidenmalonate (6) with L2b-e, L3e, and L4



Entries	Ligand	Yield (%)[a]	ee (%)[b] A.C.[c]
1	(*aR,R,R*)-**L2b**	91	62 (*R*)
2	(*aR,R,R*)-**L2c**	41	70 (*R*)
3	(*aR,R,R*)-**L2d**	66	74 (*R*)
4	(*aR,R,R*)-**L2e**	60	50 (*R*)
5	(*aS,R,R*)-**L3e**	97	20 (*S*)
6	(*aR,R,R*)-**L4**	96	68 (*R*)

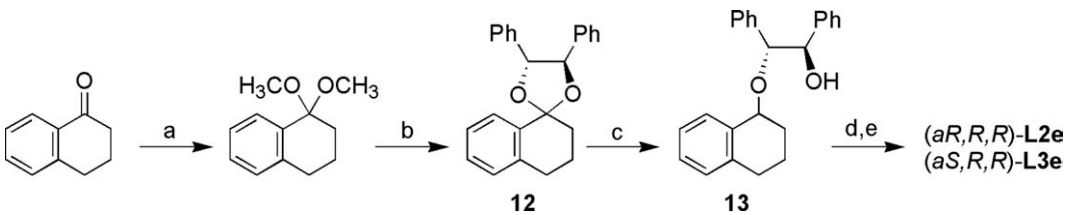
[a]Isolated yield.
[b]Determined by chiral HPLC analysis of the corresponding monoester **7**.
[c]Determined from sign of optical rotation of the corresponding monoester **7** (see Ref. 11).

The presence of only one diastereoisomer of **13** was also confirmed by GC–MS analysis. At present, we were not, however, able to determine the absolute configuration of the new benzylic stereogenic center. From alcohol **13** phosphites (*aR,R,R*)-**L2e** and (*aS,R,R*)-**L3e** were prepared by reaction with (*R*)- or (*S*)-BINOL, respectively (Scheme 2). ^{31}P NMR analysis of both phosphites showed the presence of a single phosphorus signal, confirming the diastereoisomeric purity of **13**. These phosphites were then tested in the asymmetric addition (Table 2, Entries 4 and 5). Unfortunately, the change of the ligand structure and also the introduction of a new chiral center gave negative effects on the efficiency of the ligand reducing the contribution to the stereoselection of the alcoholic part of the ligand. This appears clear comparing the ees obtained with the two matched and mismatched pairs, (*aR,R,R*)-**L2a** versus (*aS,R,R*)-**L3a** and (*aR,R,R*)-**L2e** versus (*aS,R,R*)-**L3e** (Table 1 Entries 6, 9 and Table 2 Entries 4, 5). Then we prepared phosphite (*aR,R,R*)-**L4** from 1,2-di(2-naphthyl)-1,2-ethane-1,2-diol (**8b**),[21] following the same procedure described above for analogous phosphites (Scheme 2). Also this ligand gave results comparable with that obtained with the other phosphites, giving the product in very high isolated yield and 68% ee.

CONCLUSIONS

With this investigation, we have shown that the changes of steric hindrance introduced in the alcoholic part of phoshite (*aR,R,R*)-**L2a** generally do not improve the efficiency of the ligand in the copper-catalyzed asymmetric addition of dimethylzinc to 3-phenylpropylidenemalonate (**6**). In fact, only (*aR,R,R*)-**L2d**, in which the benzylic group of (*aR,R,R*)-**L2a** has been replaced by a biphenylmethyl moiety, provided a slightly better enantioselectivity. Although this ligand appears competitive in this reaction with respect to other ligands reported in the literature,[11] giving rise to the addition product with a 74% ee and a very good yield (93%), we believe that further structural changes on this very tunable ligand could have positive effects on its efficiency as chiral inducer.

Moreover, a new simple route to floral fragrances Phenoxanol, Nitrile, and Nitrile Citralis, based on this reaction as asymmetric step, has been also disclosed. This synthetic strategy could represent a new convenient enantioselective access not only to the above cited fragrances but also to a range of structurally diverse 3-alkyl substituted esters, alcohols, aldehydes, and nitriles in optically active form.



Scheme 3. Reagent and conditions: (**a**) $CH(OCH_3)_3$, *p*-TsOH, methanol, r.t.; (**b**) (*R,R*)-1,2-diphenylethane-1,2-diol, *p*-TsOH, molecular sieves (4Å), $CHCl_3$, r.t.; (**c**) DIBAL, CH_2Cl_2, 0°C; (**d**) PCl_3, Et_3N, toluene, −60°C; (**e**) DMAP, (*R*) or (*S*)-BINOL, toluene, −60°C.

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