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TARTROL-derived chiral phosphine–phosphite ligands and their performance in enantioselective Cu-catalyzed 1,4-addition reactions

Mehmet Dindaroğlu [a], Sema Akyol [a], Hamza Şimşir [a], Jörg-Martin Neudörfl [a], Anthony Burke [b], Hans-Günther Schmalz [a,*]

[a] *Department of Chemistry, University of Cologne, Greinstrasse 4, 50939 Köln, Germany*
[b] *Department of Chemistry and Centro de Química de Evora, Universidade de Evora, Rua Romão Ramalho, 59 7000 Evora, Portugal*

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ABSTRACT

By using (*R,R,R,R*)-2,3-dimethoxy-2,3-dimethyl-1,4-dioxane-5,6-bis-diphenylmethanol (TARTROL) as a chiral building block, a set of six modular phosphine–phosphite ligands (with a 1,2-phenylene backbone) were synthesized and evaluated in the Cu-catalyzed asymmetric 1,4-addition of Grignard reagents to cyclohexenone. Ligands with bulky substituents at the *ortho*- and *para*-positions to the chiral phosphite moiety were found to be the most selective affording the 1,4-addition products with enantioselectivities of up to 84% ee.

1. Introduction

Over the past few decades, chiral bidentate phosphorous ligands have evolved as indispensable tools in asymmetric transition metal catalysis.[1] While C_2-symmetric bis-phosphine ligands such as BINAP[2] are certainly most prominent, the electronic differentiation of the two ligand teeth is an advantage in many cases.[2] Ligands containing phosphite moieties have also demonstrated their usefulness in various applications.[3]

In this context, our group has introduced modular chiral phosphine–phosphite ligands (of type **L*** (Fig. 1),[4] some of which were found to perform extremely well in a variety of transition metal-catalyzed reactions.[5–10]

While the modular architecture of these ligands opens up a easy structural variation, we had so far mainly focused on compounds prepared from TADDOL[11] or BINOL[12] as chiral building blocks. Herein we describe a new series of such ligands (of type **1**) employing TARTROL[13,14] **2** as a chiral diol (Fig. 2). In contrast to TADDOL, which contains a more flexible 1,3-dioxol ring, the two OH-substituted carbon atoms in **2** are pre-oriented in a defined 1,2-di-equatorial position at the central 1,4-dioxane ring.

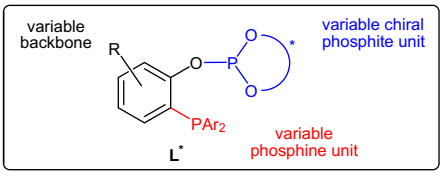


Figure 1. General structure of modular phosphine–phosphite ligands **L***.

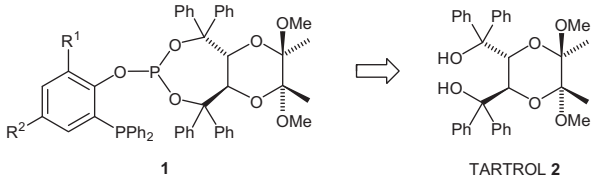
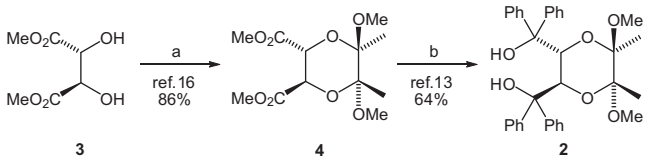


Figure 2. TARTROL-derived chiral phosphine–phosphite ligands of type **1**.

2. Results and discussion

2.1. Ligand synthesis and characterization

Following slightly modified literature protocols, the preparation of **2** was accomplished as shown in Scheme 1. According to Ley[15] the reaction of L-(+)-dimethyl tartrate **3** with 2,3-butanedione



Scheme 1. Synthesis of TARTROL **2**. Reagents: (a) 2,3-butanedione, $HC(OMe)_3$, camphorsulfonic acid, MeOH; (b) PhMgBr, THF.

* Corresponding author.
E-mail address: Schmalz@uni-koeln.de (H.-G. Schmalz).

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and trimethyl orthoformate in methanol in the presence of camphorsulfonic acid[16] proceeded stereoselectively to afford the crystalline 1,4-dioxane derivative **4** in high yield. The relative configuration of **4** was confirmed by X-ray crystal structure analysis (Fig. 3).[17] As expected for stereoelectronic reasons,[15] both methoxy groups are in an axial position at the 1,4-dioxane chair. Treatment of diester **4** with an excess of phenylmagnesium bromide then afforded **2**, which crystallized as a 1:1 clathrate with diethyl ether as proven by X-ray crystallography. This structure (Fig. 4)[18] also displays an intramolecular hydrogen bond between the two OH-groups and, again, a 1,2-diaxial orientation of the methoxy groups.

According to our general scheme,[4] the ligand synthesis (Scheme 2) commenced with the preparation of the air-stable and crystalline borane-protected phosphanylphenols **8a–f**. Starting

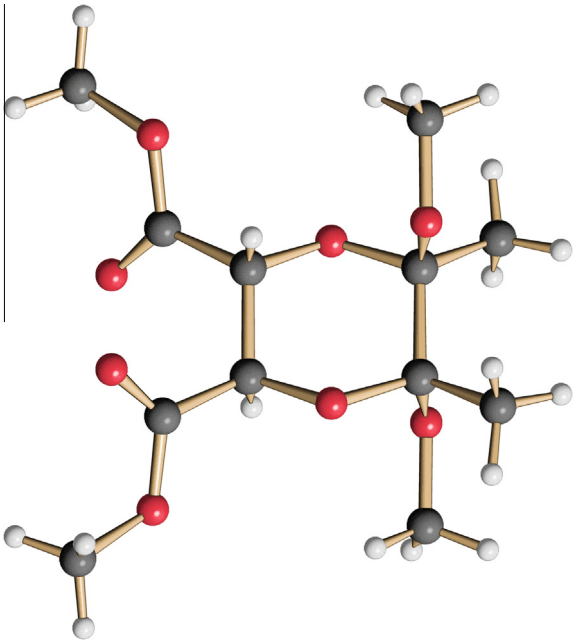


Figure 3. Structure of **4** in the crystal.[17]

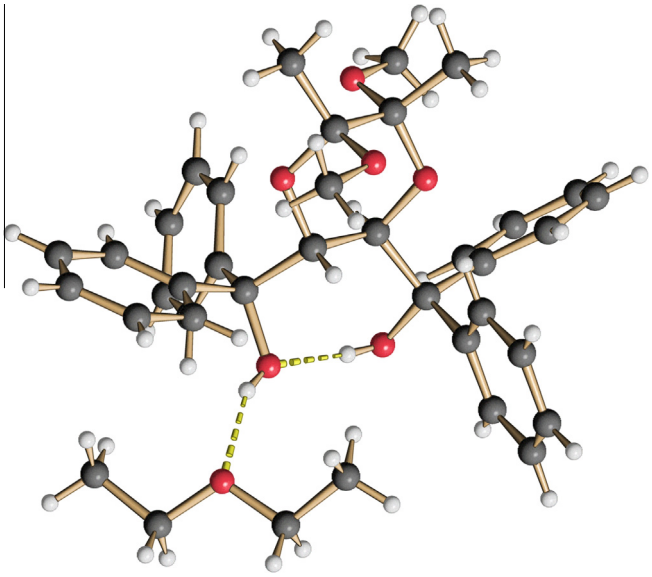
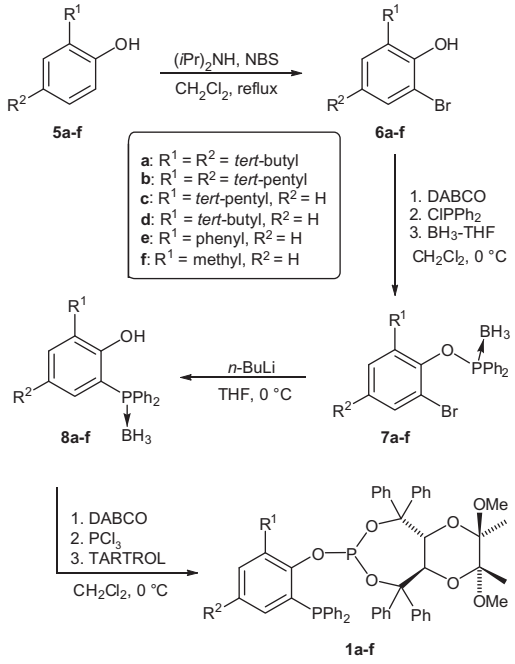


Figure 4. Structure of TARTROL **2** Et_2O in the crystal.[18]



Scheme 2. Synthesis of TARTROL-derived chiral ligands **1a–f**.

from different commercial phenols **5a–f**, the building blocks **8** were obtained in only three preparative steps by *ortho*-bromination, *O*-phosphanylation, and *n*-BuLi-initiated migration of the BH_3-protected phosphanyl unit onto the adjacent carbon center.[4]

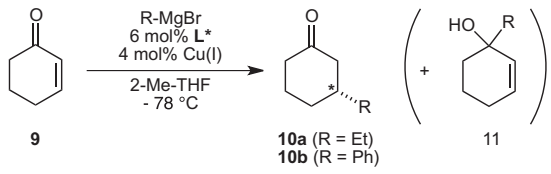
The final assembly of the ligands was then achieved by the reaction of phenols **8a–f** with PCl_3 and subsequently with TARTROL **2** in the presence of DABCO as a base. After chromatographic purification, ligands **1a–f** were obtained in 46–62% yields on a multigram scale (for details see Section 4).

2.2. Cu-catalyzed 1,4-addition using ligands of type 1

As a first functional characterization of the TARTROL-based ligands **1a–f**, we studied their performance in the asymmetric Cu-catalyzed 1,4-addition of Grignard reagents to cyclohexenone **9** (Scheme 3).[19] This reaction system was selected because the related TADDOL-derived ligands had given excellent enantio- and regioselectivity in such transformations.[5]

Using either ethyl- or phenyl-magnesium bromide, ligand screening was performed under standard reaction conditions (4 mol % of CuBr-SMe_2, 6 mol % of **L***, 2-Me-THF, −78 °C, slow addition of Grignard reagent, 2 h) on a 0.3 mmol scale. The yield and the enantiomeric composition of the products were analyzed by GC.[20] The absolute configuration of the major enantiomer was assigned by correlating the relative retention times with reference data.[5a]

As Table 1 indicates, the TARTROL-derived ligands **1a** and **1b** carrying bulky *tert*-butyl or *tert*-pentyl substituents performed



Scheme 3. Cu-catalyzed 1,4-addition of Grignard reagents to cyclohexenone **9** in the presence of chiral ligands **L***.

Table 1
Performance of TARTROL-based chiral ligands **L*** in the enantioselective 1,4-addition of Grignard reagents to cyclohexenone **9**

Entry	L*	R	Yield[a] (%)	**10**:**11**[a]	ee[b] %	Config.[c]
1	**1a**	Et	61	85:15	84	(*R*)
2	**1b**	Et	55	80:20	80	(*R*)
3	**1c**	Et	57	82:18	60	(*R*)
4	**1d**	Et	63	84:16	78	(*R*)
5	**1e**	Et	65	92:08	30	(*R*)
6	**1f**	Et	52	83:17	76	(*R*)
7	**1a**	Ph	73	86:14	14	(*S*)
8	**1b**	Ph	75	89:11	10	(*S*)
9	**1c**	Ph	82	90:10	8	(*S*)
10	**1d**	Ph	68	86:14	4	(*S*)
11	**1e**	Ph	78	92:08	4	(*S*)
12	**1f**	Ph	46	67:33	10	(*S*)

[a] Determined by GC.
[b] Determined by GC on a chiral stationary phase (BGB 176 SE).
[c] Assigned by comparison with reference samples.

quite well, at least when Et-MgBr was used as a reagent. In the best case, the 1,4-addition product **10a** was obtained with 84% ee and a reasonable level of regioselectivity (85:15). The substitution pattern on the aromatic ligand backbone had a pronounced influence on the ligand performance. However, in contrast to the related TADDOL-derived systems[5] none of the TARTROL-based ligands tested allowed the transfer of a phenyl group with a useful level of enantioselectivity. It is interesting to note that in all of the cases investigated, the TARTROL-based ligands **1a–f** preferentially afforded the opposite enantiomers of the 1,4-addition products compared to the corresponding TADDOL-derived ligands [also synthesized from the (*R*,*R*)-tartrate **3**]. This once again demonstrates the influence of ligand geometry (and conformational flexibility) on the reactivity and selectivity of the resulting metal complexes.

3. Conclusion

As an expansion of our library of modular chiral phosphine phosphites, we have synthesized and characterized a set of six new ligands of type **1** employing TARTROL **2** as a chiral diol building block. X-ray crystal structure analysis of **2** and of its precursor **4** confirmed that the 1,4-dioxane ring of this compound adopted a chair conformation with the OMe groups in the axial position. In contrast to their TADDOL-derived congeners, the new ligands did not exhibit superior properties in the Cu-catalyzed 1,4-addition of Grignard reagents to cyclohexenone. However, we are confident that some of these ligands will prove useful in other transition metal-catalyzed reactions in the future.

4. Experimental

4.1. General information

All reactions were carried out under an argon atmosphere in flame-dried glassware using Schlenk techniques. Solvents were dried as follows: THF and 2-Me-THF were distilled from sodium/benzophenone under an argon atmosphere; CH_2Cl_2 was refluxed over and distilled from CaH_2 under an argon atmosphere; MeOH was refluxed over and distilled from magnesium turnings/iodine under an argon atmosphere. L-(+)-Dimethyl tartrate (99%), 2,3-butanedione (99%), DL-10-camphorsulfonic acid (98%), trimethyl orthoformate (99%), phosphorus trichloride (PCl_3) (2 m in CH_2Cl_2), phenylmagnesium bromide (1.0 M in THF), phenylmagnesium bromide (2.8 M in 2-Me-THF), ethylmagnesium bromide (3.2 M in 2-Me-THF), and copper(I) bromide–dimethyl sulfide complex ($CuBr–SMe_2$) (99%) were purchased from Acros and used as received. 1,4-Diazabicyclo-[2.2.2]octane (DABCO) was purchased from Alfa Aesar (98%) and purified by sublimation (50 °C, 0.06 mmHg) before use. 2-Cyclohexenone (97%) was purchased from Acros, distilled and stored under argon.

^1H, ^{13}C and ^{31}P NMR spectra were recorded at room temperature in $CDCl_3$ on Bruker instruments (Avance DPX300 or Avance AV300). Chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane using the residual solvent resonance as an internal standard ($CDCl_3$: 7.24 ppm for ^1H NMR, 77.0 ppm for ^{13}C NMR). Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants (J) are presented as absolute values in Hz. IR spectra were recorded on a Perkin–Elmer Paragon 1000 FT-IR spectrometer in ATR mode at rt. Mass spectra (ESI) was recorded on a Finnigan instrument MAT 900. Melting points were determined on a Büchi B-545 instrument. Analytical TLC was carried out using precoated silica gel plates (Merck TLC plates, silica gel 60-F254). Flash column chromatography was performed using Merck silica gel 60 (40–63 μm). Optical rotations were determined on a Perkin–Elmer 343 polarimeter, concentrations (c) are given in g/100 mL.

4.2. General procedure I: synthesis of chiral phosphine phosphite ligands 1a–f

Under an argon atmosphere, a flame-dried Schlenk-flask was charged with borane-protected phosphine **8a–f** (1.0 equiv), DABCO (8.0 equiv) and CH_2Cl_2. The resulting solution was stirred for 10 min at room temperature, then cooled to 0 °C before PCl_3 (2 M in CH_2Cl_2, 1.2 equiv) was added dropwise via syringe over 30 min. The resulting slurry was stirred for 30 min at this temperature, then allowed to warm to room temperature and stirred for another 3 h. The reaction mixture was cooled again to 0 °C and a solution of TARTROL **2** (1.5 equiv) in CH_2Cl_2 was added dropwise via syringe over 30 min. The resulting suspension was stirred for 30 min at 0 °C, then allowed to warm to room temperature and stirred for another 20 h. The reaction mixture was filtered over silica gel. After concentration of the filtrate by rotary evaporation under reduced pressure, the crude product was purified by flash column chromatography on silica gel, eluting with cyclohexane/CH_2Cl_2. The desired ligands were obtained as a white foam.

4.3. General procedure II: 1,4-addition reactions

Under an argon atmosphere, a chiral ligand (0.018 mmol, 0.06 equiv) and $CuBr–SMe_2$ (0.012 mmol, 0.04 equiv) were dissolved in 1.5 mL of dry 2-Me-THF and the solution was stirred for 15 min at room temperature. After addition of 2-cyclohexenone (0.3 mmol, 1.0 equiv), the mixture was stirred for 15 min before it was cooled to −78 °C. Then a dilute solution of the Grignard reagent (0.36 mmol, 1.2 equiv, in 1 mL 2-Me-THF) was added slowly via syringe pump over 2 h. The mixture was stirred at −78 °C for another 1 h and then quenched by the slow, successive addition of MeOH (1 mL) and saturated aqueous NH_4Cl solution (2 mL). The layers were separated and the organic phase was analyzed by GC on a chiral stationary phase.[20]

4.4. (2*R*,3*R*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-1,4-dioxane-2,3-dicarboxylic acid dimethyl ester 4

Under an argon atmosphere 17.82 g (100 mmol, 1.0 equiv) of L-(+)-dimethyl tartrate **3** and 1.16 g (5 mmol, 0.05 equiv) of camphorsulfonic acid were dissolved in 100 ml of dry methanol. To this solution was added 10.33 ml (120 mmol, 1.2 equiv) of 2,3-butanedione and 44 ml (400 mmol, 4.0 equiv) of trimethyl orthoformate. The reaction mixture was then heated at reflux for 24 h. After cooling to room temperature, 16 g of $NaHCO_3$ was added to the dark

red solution and stirring was continued for 15 min. The mixture was filtered and concentrated under reduced pressure by rotary evaporation. The crude product was purified by flash column chromatography on silica gel with cyclohexane/EtOAc (5:1) to give product **4** as a white solid (25.1 g, 86 mmol, 86%). A sample used for X-ray analysis was re-crystallized from cyclohexane. R_f = 0.25 (cyclohexane/EtOAc, 5:1), mp = 108 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.51 (s, 2H, CH), 3.74 (s, 6H, CO_2CH_3), 3.30 (s, 6H, $COCH_3$), 1.33 (s, 6H, CH_3). ^{13}C NMR (APT, 75 MHz, $CDCl_3$): δ = 168.4 (CO_2CH_3), 99.2 (C_q), 68.7 (CH), 52.5 (CO_2CH_3), 48.4 ($COCH_3$), 17.3 (CH_3). IR (neat): 2992, 2951, 2835, 1742, 1437, 1377, 1359, 1285, 1200, 1172, 1110, 1032, 950, 886, 853, 809, 773, 741 cm^{-1}. HRMS (ESI): m/z = [M+Na]$^+$: 315.1045 (calcd: m/z = 315.1050).: $[\alpha]_{589}^{20} = -140.6$ (c 1.0, $CHCl_3$), $[\alpha]_{546}^{20} = -166.0$ (c 1.0, $CHCl_3$), $[\alpha]_{405}^{20} = -324.7$ (c 1.0, $CHCl_3$), $[\alpha]_{365}^{20} = -413.8$ (c 1.0, $CHCl_3$).

4.5. (2*R*,3*R*,5*R*,6*R*)-2,3-Bis(hydroxydiphenylmethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane 2 (TARTROL)

Under an argon atmosphere 90.2 ml (90.2 mmol, 4.4 equiv) of phenylmagnesium bromide (1 M in THF) was placed in a 250 ml Schlenk-flask and cooled to 0 °C. To this Grignard solution was slowly added 6.0 g (20.5 mmol, 1.0 equiv) of diester **4** in 80 ml of dry THF. After completion of the addition, the reaction mixture was heated at reflux for 2 h and then stirred at room temperature for 18 h. Then the mixture was hydrolyzed under cooling in an ice/water bath by the careful addition of 200 ml of aqueous saturated NH_4Cl solution. A precipitate, initially formed during the hydrolysis, was re-dissolved under intense stirring. Next, 10% aqueous HCl was added until the pH was in the range of 7–8. The orange organic layer was separated, and the aqueous layer was extracted three times with 100 mL of EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the resulting crude product was purified by flash column chromatography on silica gel with cyclohexane/EtOAc (20:1) to afford TARTROL **2** as a white foam (7.1 g, 13.1 mmol, 64%). A sample used for X-ray analysis was re-crystallized from ether. R_f = 0.28 (cyclohexane/EtOAc, 10:1), mp = 96 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98–7.96 (m, 4H, CH_{Ar}), 7.44–7.22 (m, 6H, CH_{Ar}), 7.14–7.02 (m, 10H, CH_{Ar}), 4.38 (s, 2H, CH), 4.33 (s, 2H, OH), 2.57 (s, 6H, OCH_3), 0.99 (s, 6H, CH_3). ^{13}C NMR (APT, 75 MHz, $CDCl_3$): δ = 146.0 (C_{qAr}), 142.8 (C_{qAr}), 127.9 (CH_{Ar}), 127.7 (CH_{Ar}), 127.2(CH_{Ar}), 127.1 (CH_{Ar}), 126.8 (CH_{Ar}), 98.5 ($COCH_3$), 79.4 (COH), 75.9 (CH), 47.6 ($COCH_3$), 17.1 (CH_3). IR (neat): 3355, 3057, 3021, 2992, 2943, 2830, 2244, 1598, 1491, 1446, 1371, 1318, 1122, 1034, 908, 847 cm^{-1}. HRMS (ESI): m/z = [M+Na]$^+$: 563.2400 (calcd: m/z = 563.2404). $[\alpha]_{589}^{20} = +50.6$ (c 1.0, $CHCl_3$), $[\alpha]_{546}^{20} = +62.0$ (c 1.0, $CHCl_3$), $[\alpha]_{405}^{20} = +154.1$ (c 1.0, $CHCl_3$), $[\alpha]_{365}^{20} = +226.0$ (c 1.0, $CHCl_3$).

4.6. (2*R*,3*R*,4a*R*,9a*R*)-7-(2,4-Di-*tert*-butyl-6-diphenylphosphino-phenoxy)-2,3-dimethoxy-2,3-dimethyl-5,5,9,9-tetraphenyl-hexahydro-[1,4]dioxino[2,3-*e*][1,3,2]-dioxaphosphepine 1a

According to general procedure I, phosphine **8a** (2.02 g, 5.0 mmol) was reacted with DABCO (4.49 g, 40.0 mmol) and PCl_3 (3.0 mL, 6.0 mmol) in 25 mL of CH_2Cl_2 before diol **2** (4.05 g, 7.5 mmol) in 25 mL of CH_2Cl_2 was added. The crude product was purified by flash column chromatography (cyclohexane/CH_2Cl_2, 4:1) to afford **1a** (2.97 g, 3.1 mmol, 62%) as a white foam. R_f = 0.4 (cyclohexane/CH_2Cl_2, 4:1), mp = 115–120 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (s, 2H, H_{Ar}), 7.51 (d, J = 7.6 Hz, 2H, H_{Ar}), 7.33–7.04 (m, 21H, H_{Ar}), 6.94–6.79 (m, 6H, H_{Ar}), 6.70 (dd, J = 3.6 Hz, 2.6 Hz, 1H, H_{Ar}), 4.86 (d, J = 10.8 Hz, 1H, CH), 4.75 (d, J = 10.8 Hz, 1H, CH), 2.60 (s, 3H, OCH_3), 2.33 (s, 3H, OCH_3), 1.20 (s, 9H, $((CH_3)_3)$), 1.07 (s, 9H, $((CH_3)_3)$), 1.06 (s, 3H, CH_3), 1.02 (s, 3H, CH_3). ^{13}C NMR (APT, 75 MHz, $CDCl_3$): δ = 147.6, 146.7, 146.6, 144.6, 141.1, 140.9, 140.8, 139.3, 139.2, 134.0, 133.7, 133.5, 131.4, 131.3, 130.7, 129.8, 128.5, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 126.6, 126.4, 126.4, 125.7, 99.0, 98.7, 86.6, 86.3, 83.0, 82.9, 75.7, 75.1, 47.6, 46.9, 35.5, 34.4, 31.2, 30.8, 17.0. ^{31}P NMR {^{1}H} (121 MHz, $CDCl_3$): δ = 138.2 (d, J = 115.8 Hz, $P(OR)_3$), −15.7 (d, J = 106.8 Hz, PR_3). IR (neat): 3054, 2957, 2868, 2831, 1583, 1492, 1476, 1445, 1432, 1418, 1391, 1372, 1361, 1283, 1258, 1202, 1128, 1029, 983, 905, 856, 837, 810, 776, 732, 694, 671, 649 cm^{-1}. HRMS (ESI): m/z = [M+Na]$^+$: 981.4015 (calcd: m/z = 981.4019). $[\alpha]_{589}^{20} = +125.7$ (c 0.5, $CHCl_3$), $[\alpha]_{546}^{20} = +153.5$ (c 0.5, $CHCl_3$), $[\alpha]_{405}^{20} = +450.2$ (c 0.5, $CHCl_3$), $[\alpha]_{365}^{20} = +764.0$ (c 0.5, $CHCl_3$).

4.7. (2*R*,3*R*,4a*R*,9a*R*)-7-(2-Diphenylphosphino-4,6-di-*tert*-pentyl-phenoxy)-2,3-dimethoxy-2,3-dimethyl-5,5,9,9-tetraphenyl-hexahydro-[1,4]dioxino[2,3-*e*][1,3,2]-dioxaphosphepine 1b

According to general procedure I, phosphine **8b** (1.97 g, 4.56 mmol) was reacted with DABCO (4.09 g, 36.48 mmol) and PCl_3 (2.8 ml, 5.47 mmol) in 25 mL of CH_2Cl_2 before diol **2** (3.70 g, 6.84 mmol) in 25 mL of CH_2Cl_2 was added. The crude product was purified by flash column chromatography (cyclohexane/CH_2Cl_2, 5:1) to afford **1b** (2.26 g, 2.29 mmol, 50%) as a white foam. R_f = 0.6 (cyclohexane/CH_2Cl_2, 2:1), mp = 118–125 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (s, 2H, H_{Ar}), 7.59 (d, J = 7.6 Hz, 2H, H_{Ar}), 7.35–6.98 (m, 23H, H_{Ar}), 6.92 (t, J = 7.2 Hz, 2H, H_{Ar}), 6.80 (t, J = 7.4 Hz, 2H, H_{Ar}), 6.61 (s, 1H, H_{Ar}), 4.84 (d, J = 11.5 Hz, 1H, CH), 4.80 (d, J = 11.6 Hz, 1H, CH), 2.70 (s, 3H, OCH_3), 2.37 (s, 3H, OCH_3), 1.86–1.63 (m, 2H, CH_2), 1.42–1.40 (m, 2H, CH_2), 1.25 (s, 6H, $(CH_3)_2$), 1.10 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 0.58 (t, J = 7.2 Hz, 3H, CH_2CH_3), 0.51 (t, J = 7.1 Hz, 3H, CH_2CH_3). ^{13}C NMR (APT, 75 MHz, $CDCl_3$): δ = 147.6, 147.5, 146.5, 146.4, 142.8, 141.0, 140.9, 139.5, 139.4, 139.2, 133.9, 133.6, 131.4, 131.3, 131.2, 129.5, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.6, 127.5, 126.6, 126.5, 126.4, 99.0, 98.6, 86.3, 86.4, 83.0, 82.9, 75.7, 75.2, 47.7, 46.8, 39.0, 37.5, 36.8, 33.2, 29.3, 28.8, 28.2, 28.0, 17.0, 9.7, 9.0. ^{31}P NMR {^{1}H} (121 MHz, $CDCl_3$): δ = 140.0 (d, J = 109.4 Hz, $P(OR)_3$), −15.0 (d, J = 109.3 Hz, PR_3). IR (neat): 3054, 2958, 2872, 2831, 1583, 1492, 1445, 1432, 1419, 1373, 1360, 1297, 1263, 1204, 1128, 1030, 989, 924, 905, 834, 810, 783, 770, 739, 695, 671, 649 cm^{-1}. HRMS (ESI): m/z = [M+Na]$^+$: 1009.4354 (calcd: m/z = 1009.4332). $[\alpha]_{589}^{20} = +79.5$ (c 0.5, $CHCl_3$), $[\alpha]_{546}^{20} = +99.8$ (c 0.5, $CHCl_3$), $[\alpha]_{405}^{20} = +296.5$ (c 0.5, $CHCl_3$).

4.8. (2*R*,3*R*,4a*R*,9a*R*)-7-(2-Diphenylphosphino-6-*tert*-pentyl-phenoxy)-2,3-dimethoxy-2,3-dimethyl-5,5,9,9-tetraphenyl-hexahydro-[1,4]dioxino[2,3-*e*][1,3,2]-dioxaphosphepine 1c

According to general procedure I, phosphine **8c** (1.24 g, 3.43 mmol) was reacted with DABCO (3.08 g, 27.44 mmol) and PCl_3 (2.1 ml, 4.2 mmol) in 25 mL of CH_2Cl_2 before diol **2** (2.78 g, 5.14 mmol) in 25 mL of CH_2Cl_2 was added. The crude product was purified by flash column chromatography (cyclohexane/CH_2Cl_2, 4:1) to afford **1c** (1.66 g, 1.8 mmol, 53%) as a white foam. R_f = 0.45 (cyclohexane/CH_2Cl_2, 4:1), mp = 110–115 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (s, 2H, H_{Ar}), 7.54 (d, J = 7.4 Hz, 2H, H_{Ar}), 7.31–6.98 (m, 23H, H_{Ar}), 6.88 (t, J = 6.7 Hz, 3H, H_{Ar}), 6.76 (t, J = 7.1 Hz, 2H, H_{Ar}), 6.65 (d, J = 6.6 Hz, 1H, H_{Ar}), 4.79 (d, J = 11.9 Hz, 1H, CH), 4.76 (d, J = 11.7 Hz, 1H, CH), 2.67 (s, 3H, OCH_3), 2.32 (s, 3H, OCH_3), 1.64–1.57 (m, 2H, CH_2), 1.20 (s, 6H, $(CH_3)_2$), 1.06 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 0.47 (t, J = 7.0 Hz, 3H, CH_2CH_3). ^{13}C NMR (APT, 75 MHz, $CDCl_3$): δ = 147.5, 146.3, 146.2,

133.9, 133.7, 133.2, 131.4, 131.3, 129.9, 129.4, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 127.5, 126.6, 126.5, 126.4, 123.0, 98.9, 98.6, 75.7, 75.2, 47.7, 46.8, 38.9, 33.0, 29.5, 28.9, 17.0, 9.8. ^{31}P NMR {^{1}H} (121 MHz, $CDCl_3$): δ = 140.4 (d, J = 111.2 Hz, $P(OR)_3$), −15.5 (d, J = 111.2 Hz, PR_3). IR (neat): 3053, 2953, 2872, 2830, 1583, 1492, 1445, 1432, 1400, 1373, 1301, 1264, 1203, 1140, 1128, 1030, 1014, 989, 924, 905, 837, 811, 739, 717, 696, 671 cm^{-1}. HRMS (ESI): m/z = [M+Na]$^+$: 939.3551 (calcd: m/z = 939.3550). $[\alpha]_{589}^{20}$ = +137.1 (*c* 0.5, $CHCl_3$), $[\alpha]_{546}^{20}$ = +169.0 (*c* 0.5, $CHCl_3$), $[\alpha]_{405}^{20}$ = +470.0 (*c* 0.5, $CHCl_3$), $[\alpha]_{365}^{20}$ = +777.0 (*c* 0.5, $CHCl_3$).

4.9. (2*R*,3*R*,4a*R*,9a*R*)-7-(2-*tert*-Butyl-6-diphenylphosphino-phenoxy)-2,3-dimethoxy-2,3-dimethyl-5,5,9,9-tetraphenyl-hexahydro-[1,4]dioxino[2,3-*e*][1,3,2]-dioxaphosphepine 1d

According to general procedure I, phosphine **8d** (1.74 g, 5.0 mmol) was reacted with DABCO (4.49 g, 40.0 mmol) and PCl_3 (3.0 mL, 6.0 mmol) in 25 mL of CH_2Cl_2 before diol **2** (4.05 g, 7.5 mmol) in 25 mL of CH_2Cl_2 was added. The crude product was purified by flash column chromatography (cyclohexane/CH_2Cl_2, 4:1) to afford **1d** (2.07 g, 2.30 mmol, 46%) as a white foam. R_f = 0.4 (cyclohexane/CH_2Cl_2, 4:1), mp = 115–125 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (s, 2H, H_{Ar}), 7.53 (d, J = 7.8 Hz, 2H, H_{Ar}), 7.34–7.31 (m, 5H, H_{Ar}), 7.23–7.04 (m, 16H, H_{Ar}), 6.96–6.80 (m, 7H, H_{Ar}), 6.71 (ddd, J = 7.5 Hz, 3.0 Hz, 1.6 Hz, 1H, H_{Ar}), 4.86 (d, J = 10.8 Hz, 1H, CH), 4.75 (d, J = 10.8 Hz, 1H, CH), 2.61 (s, 3H, OCH_3), 2.33 (s, 3H, OCH_3), 1.21 (s, 9H, $((CH_3)_3)$), 1.06 (s, 3H, CH_3), 1.02 (s, 3H, CH_3). ^{13}C NMR (APT, 75 MHz, $CDCl_3$): δ = 147.4, 140.9, 139.1, 133.9, 133.8, 133.7, 133.6, 133.5, 131.4, 131.3, 129.7, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.5, 126.6, 126.5, 126.4, 126.3, 123.0, 99.0, 98.7, 86.6, 86.4, 75.7, 75.1, 47.6, 46.9, 35.3, 30.7, 17.0. ^{31}P NMR {^{1}H} (121 MHz, $CDCl_3$): δ = 138.5 (d, J = 118.2 Hz, $P(OR)_3$), −16.5 (d, J = 118.2 Hz, PR_3). IR (neat): 3054, 2945, 2829, 1492, 1445, 1432, 1400, 1389, 1372, 1360, 1204, 1139, 1128, 1029, 1013, 981, 924, 904, 839, 814, 747, 695, 666, 650 cm^{-1}. HRMS (ESI): m/z = [M+Na]$^+$: 925.3391 (calcd: m/z = 925.3393). $[\alpha]_{589}^{20}$ = +189.3 (*c* 0.5, $CHCl_3$), $[\alpha]_{546}^{20}$ = +230.7 (*c* 0.5, $CHCl_3$), $[\alpha]_{405}^{20}$ = +650.9 (*c* 0.5, $CHCl_3$).

4.10. (2*R*,3*R*,4a*R*,9a*R*)-7-(3-Diphenylphosphino-biphenyl-2-yloxy)-2,3-dimethoxy-2,3-dimethyl-5,5,9,9-tetraphenyl-hexahydro-[1,4]dioxino[2,3-*e*][1,3,2]-dioxaphosphepine 1e

According to general procedure I, phosphine **8e** (1.84 g, 5.0 mmol) was reacted with DABCO (4.49 g, 40.0 mmol) and PCl_3 (3.0 mL, 6.0 mmol) in 25 mL of CH_2Cl_2 before diol **2** (4.05 g, 7.5 mmol) in 25 mL of CH_2Cl_2 was added. The crude product was purified under nitrogen by flash column chromatography (cyclohexane/CH_2Cl_2, 4:1) to afford **1e** (2.44 g, 2.64 mmol, 53%) as a white foam. R_f = 0.3 (cyclohexane/CH_2Cl_2, 2:1), mp = 115–120 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70 (d, J = 7.1 Hz, 2H, H_{Ar}), 7.52 (d, J = 7.6 Hz, 2H, H_{Ar}), 7.30–7.28 (m, 4H, H_{Ar}), 7.25–7.19 (m, 8H, H_{Ar}), 7.17–7.12 (m, 9H, H_{Ar}), 7.07–7.04 (m, 6H, H_{Ar}), 7.02–6.97 (m, 2H, H_{Ar}), 6.89 (t, J = 7.7 Hz, 2H, H_{Ar}), 6.77 (ddd, J = 7.6 Hz, 3.3 Hz, 1.7 Hz, 1H, H_{Ar}), 6.29 (d, J = 7.3 Hz, 2H, H_{Ar}), 4.64 (d, J = 10.7 Hz, 1H, CH), 4.49 (d, J = 10.7 Hz, 1H, CH), 2.50 (s, 3H, OCH_3), 2.30 (s, 3H, OCH_3), 1.03 (s, 3H, CH_3), 1.02 (s, 3H, CH_3). ^{13}C NMR (APT, 75 MHz, $CDCl_3$): δ = 152.7, 152.6, 152.5, 152.4, 147.0, 146.9, 141.1, 139.5, 139.4, 138.2, 138.1, 137.1, 137.0, 136.4, 136.3, 135.2, 135.1, 134.2, 134.1, 133.9, 133.8, 133.7, 132.3, 131.3, 131.2, 131.1, 130.9, 130.8, 130.4, 129.8, 128.6, 128.3, 128.2, 127.8, 127.5, 127.3, 126.7, 126.6, 126.4, 125.9, 124.0, 98.8, 98.6, 86.3, 86.2, 82.6, 82.5, 75.3, 74.7, 47.4, 46.9, 17.0, 16.9. ^{31}P NMR {^{1}H} (121 MHz, $CDCl_3$): δ = 137.1 (d, J = 106.4 Hz, $P(OR)_3$), −15.9 (d, J = 106.4 Hz, PR_3). IR (neat): 3053, 2945, 2830, 1599, 1581, 1492, 1445, 1432, 1402, 1372, 1203, 1127, 1030, 982, 907, 843, 819, 765, 740, 696, 671 cm^{-1}. HRMS (ESI): m/z = [M+Ag]$^+$: 1029.2230 (calcd: m/z = 1029.2239). $[\alpha]_{589}^{20}$ = +219.1 (*c* 0.5, $CHCl_3$), $[\alpha]_{546}^{20}$ = +269.4 (*c* 0.5, $CHCl_3$).

4.11. (2*R*,3*R*,4a*R*,9a*R*)-7-(2-Diphenylphosphino-6-methyl-phenoxy)-2,3-dimethoxy-2,3-dimethyl-5,5,9,9-tetraphenyl-hexahydro-[1,4]dioxino[2,3-*e*][1,3,2]-dioxaphosphepine 1f

According to general procedure I, phosphine **8f** (1.53 g, 5.0 mmol) was reacted with DABCO (4.49 g, 40.0 mmol) and PCl_3 (3.0 mL, 6.0 mmol) in 25 mL of CH_2Cl_2 before diol **2** (4.05 g, 7.5 mmol) in 25 mL of CH_2Cl_2 was added. The crude product was purified by flash column chromatography (cyclohexane/CH_2Cl_2, 4:1) to afford **1f** (2.19 g, 2.54 mmol, 51%) as a white foam. R_f = 0.3 (cyclohexane:CH_2Cl_2, 4:1), mp = 125–130 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, J = 8.0 Hz, 2H, H_{Ar}), 7.66 (t, J = 7.9 Hz, 3H, H_{Ar}), 7.48–7.39 (m, 2H, H_{Ar}), 7.33–7.26 (m, 7H, H_{Ar}), 7.19–7.16 (m, 6H, H_{Ar}), 7.12–6.99 (m, 11H, H_{Ar}), 6.85 (t, J = 7.5 Hz, 1H, H_{Ar}), 6.55 (ddd, J = 7.3 Hz, 3.0 Hz, 1.3 Hz, 1H, H_{Ar}), 4.75 (d, J = 10.9 Hz, 1H, CH), 4.70 (d, J = 10.9 Hz, 1H, CH), 2.67 (s, 3H, OCH_3), 2.33 (s, 3H, OCH_3), 2.14 (s, 3H, Ph-CH_3), 1.07 (s, 3H, CH_3), 1.00 (s, 3H, CH_3). ^{13}C NMR (APT, 75 MHz, $CDCl_3$): δ = 146.1, 146.0, 140.9, 140.8, 134.4, 134.1, 133.8, 131.8, 131.7, 131.4, 131.2, 131.1, 129.8, 128.5, 128.3, 128.2, 128.1, 127.9, 127.7, 127.5, 127.2, 126.9, 126.7, 126.6, 126.4, 125.6, 123.8, 98.9, 98.6, 86.5, 82.6, 75.5, 75.0, 47.7, 46.9, 17.0. ^{31}P NMR {^{1}H} (121 MHz, $CDCl_3$): δ = 139.3 (d, J = 69.4 Hz, $P(OR)_3$), −16.6 (d, J = 69.4 Hz, PR_3). IR (neat): 3054, 2945, 2830, 1583, 1491, 1445, 1433, 1408, 1373, 1255, 1205, 1176, 1140, 1128, 1030, 984, 925, 906, 874, 840, 817, 740, 696, 671 cm^{-1}. HRMS (ESI): m/z = [M+Na]$^+$: 883.2925 (calcd: m/z = 883.2924). $[\alpha]_{589}^{20}$ = +113.3 (*c* 0.5, $CHCl_3$), $[\alpha]_{546}^{20}$ = +138.5 (*c* 0.5, $CHCl_3$), $[\alpha]_{405}^{20}$ = +375.1 (*c* 0.5, $CHCl_3$), $[\alpha]_{365}^{20}$ = +598.2 (*c* 0.5, $CHCl_3$).

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17. *X-ray crystal structure of* ***4***: Formula: $C_{12}H_{20}O_8$, crystal size: 0.3 × 0.2 × 0.1 mm; orthorhombic; space group $P2_122_1$; 100 K; λ = 0.71073 Å; unit cell: a = 7.5641(4) Å, b = 9.1334(6) Å, c = 10.3354(7) Å; V = 714.03(8) Å^3; Z = 2; d (calcd) = 1.359 g/cm^3; F(0 0 0) 312; Θ-range: 2.23°–26.99°; 933 independent reflexes; R indices [$I > 2\sigma$ (I)]: R_1 = 0.0265, wR_2 = 0.0680; residual electron density: 0.185 and −0.172 eÅ^3. Structure determination with direct methods (SHELXS). CCDC 911862 contains the Supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
18. *X-ray crystal structure of* ***2*** *Et_2O*: Formula: $C_{38}H_{46}O_7$, crystal size: 0.4 × 0.3 × 0.3 mm; orthorhombic; space group $P2_12_12_1$; 100 K; λ = 0.71073 Å; unit cell: a = 9.7760(5) Å, b = 11.4835(6) Å, c = 30.0220(15) Å; V = 3370.4(3) Å^3; Z = 4; d (calcd) = 1.212 g/cm^3; F(0 0 0) 1320; Θ-range: 1.36°–27.00°; 4109 independent reflexes; R indices [$I > 2\sigma$ (I)]: R_1 = 0.0394, wR_2 = 0.0788; residual electron density: 0.182 and -0.209 eÅ^3. Structure determination with direct methods (SHELXS). CCDC 911863 contains the Supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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20. 1,4-Addition reactions were monitored by GC–MS using an Agilent GC 6890N gas chromatograph equipped with a Hewlett Packard 5973N mass selective detector. Enantiomeric ratios were determined by chiral GC analysis using an Agilent GC 6890N gas chromatograph and a BGB 176 SE column (30 m × 0.25 mm).