Tetrahedron: Asymmetry Vol. 4, No. 7, pp. 1625-1634, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00

Rhodium Catalysed Asymmetric Hydroformylation with Chiral Diphosphite Ligands

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(*Received in UK* 2 *April* 1993; *accepted* 12 *May* 1993)

Abstract: Chiral diphosphites have been synthesised starting from 1,2:5,6-diisopropylidene-*D*-mannitol, *L*-α,α,α,α,-tetramethyl-1,3-dioxolan-4,5-dimethanol and *L*-diethyltartrate. The diols react in moderate to good yields with 2,2'-bisphenoxyphosphorus chloride and 4,4',6,6',-tetra-*t*-butyl-2,2'-bisphenoxyphosphorus chloride (32-92%) to the corresponding chiral diphosphites. These compounds all exhibit C_2 symmetry and have been used as ligands in the rhodium catalysed asymmetric hydroformylation of styrene. The catalytic activity of the diphosphites strongly depends on the bulkyness of the ligand. With a bulky ligand enantiomeric excesses up till 20 % have been obtained under mild reaction conditions (25-40°C, 40 bar syngas). It was found that both enantiomeric excess and regioselectivity to the branched aldehyde strongly depend on the hydroformylation reaction conditions.

INTRODUCTION

Asymmetric hydroformylation is a convenient synthetic method for obtaining optically active aldehydes from olefinic substrates.[1,2] These aldehydes are attractive as chiral building blocks in organic synthesis. For example, 2-arylpropionic acids, which can be synthesised by oxidation of the corresponding aldehydes, represent a class of anti inflammatory reagents with considerable pharmaceutical and commercial interest.[3] Styrene and other vinyl aromatics have been widely used as model substrates in the asymmetric hydroformylation because the products resemble precursors in the pharmaceutical industry (figure 1).[4,5] In general only one of the two enantiomers is responsible for the desired biological activity. For industrial applicability a high enantiomeric excess and an almost exclusive chemoselectivity to the branched aldehyde is needed.[1,6]

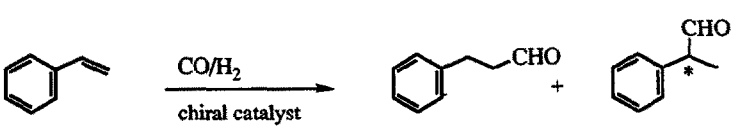


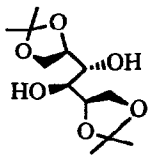
figure 1. Asymmetric hydroformylation of styrene

Since the early seventies both chiral rhodium and platinum complexes have been used as catalysts in the asymmetric hydroformylation of functionalised alkenes.[7-9] Most reports concern the use of chiral mono and diphosphine compounds as ligands. Recently high enantioselectivities have been reported with platinum/-diphosphine catalysts in the hydroformylation of functionalised alkenes. Unfortunately the reaction conditions generally are severe and the chemoselectivity and the regioselectivity for the branched aldehyde is much lower than that obtained with rhodium catalysts.[5,10,11] A drawback of the rhodium catalysed asymmetric hydroformylation is the low enantiomeric excess obtained up till now. Surprisingly only scarce attention has been given to phosphites as ligands in the asymmetric hydroformylation. These ligands are relatively easy to prepare from readily available starting material and they are less prone to oxidation compared with phosphines.

In 1975, for the first time, a chiral mono phosphite was used in the asymmetric hydroformylation.[12] The ligand was based upon menthol but no enantiomeric excesses could be induced in the asymmetric hydroformylation of styrene, α-methylstyrene and α-ethylstyrene. Phosphite ligands based on chiral diols have also been used as ligands in the asymmetric hydroformylation of styrene but no asymmetric induction could be obtained.[13] Successful asymmetric hydroformylation with vinyl acetate using chiral diphosphite ligands has been reported recently.[14] In the whole field of asymmetric hydroformylation the highest obtained enantioselectivities with rhodium catalysts reported are very disappointing up till now (e.g. about 30% and 60% in the case of styrene and methyl N-acetamidoacrylate respectively), but the chemoselectivity and regioselectivity for the branched aldehyde are encouraging.[15,16] We are the first to report the asymmetric hydroformylation of styrene with several new chiral diphosphite ligands having C_2 symmetry. Enantiomeric excesses up till 20% and high regioselectivity to the branched aldehyde have been obtained. Especially bulky diphosphite ligands seemed of interest because they usually lead to highly active systems.[17, 18]

RESULTS AND DISCUSSION

Optically active diols are useful building blocks for the synthesis of chiral diphosphite ligands. We have used the optically pure enantiomers 1,2:5,6-diisopropylidene-*D*-mannitol (**1**), *L*-α,α,α',α'-tetramethyl-1,3-dioxolan-4,5-dimethanol (**2**) and *L*-diethyltartrate (**3**) as starting materials for the synthesis of our chiral diphosphite ligands (figure 2).



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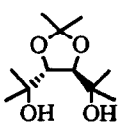

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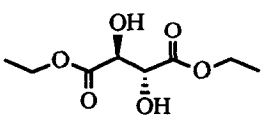
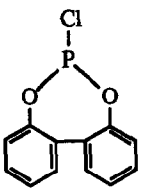


3

figure 2. Chiral diols with C_2 symmetry

These diols react in moderate to good yields (32-92%) with the 2,2'-bisphenoxy phosphorus chlorides **4** and **5** (figure 3) to the corresponding diphosphite ligands **1a**, **2a**, **3a** and **3b** (figure 4) in the presence of pyridine or triethylamine. The phosphorus chlorides are based upon 2,2'-bisphenols with or without *t*-butyl substituents at the ortho and para positions.



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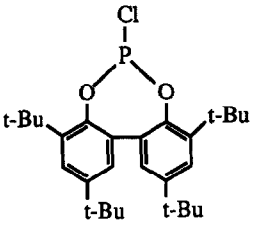

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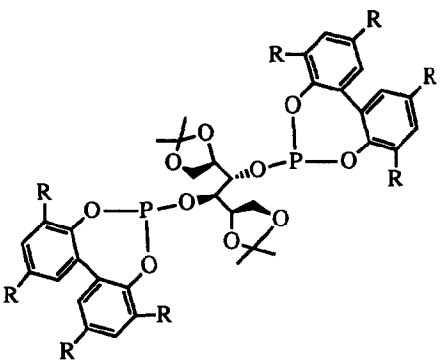
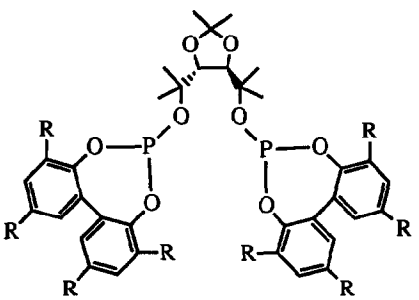
figure 3. Bisphenoxy phosphorus chlorides

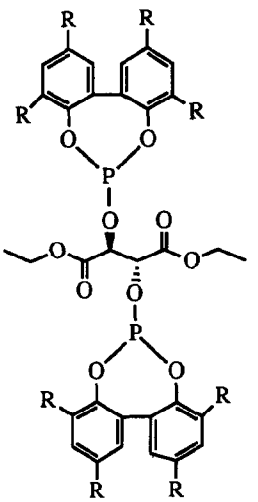
The optically pure diphosphites all exhibit C_2 symmetry but differ in the number of bonds between the two phosphorus atoms. We introduced *t*-butyl substituents in order to increase the steric hindrance of the ligands (figure 4). The *t*-butyl substituents at the para positions could give rise to axial chirality but this was neither observed in **5** nor in the related ligand with ^{31}P and ^{1}H NMR.



1a. (3R,4R), R=H
1b. (3R,4R), R=t-Bu



2a. (2R,3R), R=H
2b. (2R,3R), R=t-Bu



3a. (2R,3R), R=H
3b. (2R,3R), R=t-Bu

figure 4. Chiral diphosphite ligands with C_2 symmetry

The ligands were all stable on silica gel under an atmosphere of argon and were isolated as white solids. We were not successful in the synthesis of the tetra-4,4',6,6'-*t*-butyl substituted 2,2'-bisphenol analogues **1b** and **2b** probably as a consequence of too much steric hindrance of the bulky *t*-butyl substituents; mono substituted diols were formed in the presence of a considerable amount of hydrolysed phosphorus chlorides.

The results of the rhodium catalysed hydroformylation of styrene with the chiral diphosphite ligands **1a**, **2a**, **3a** and **3b** are reported in table 1. Two experiments (run 1 and 2) were carried out without the addition of any ligand. Under these conditions we expect the formation of a $HRh(CO)_4$ species. This catalytic species is very active but shows a low regioselectivity to the branched aldehyde. Addition of a 10-fold excess of **1a** or **3a** kills the activity of the catalysts (runs 3 and 5). With a 10-fold excess of **2a**, a very low catalytic activity remains (run 4). The good binding abilities of **1a**, **2a** and **3a** probably prevents coordination of styrene to rhodium. The decreasing catalytic activity when a 10-fold excess of **1a**, **2a** or **3a** was used, is probably a consequence of the formation of a fully saturated rhodium species. When a small excess of ligand was used, hardly any enantiomeric excesses were obtained with **2a** and **3a** (runs 7 and 8) which could be caused by the less bulky and flexible structure of these ligands. We therefore turned to the more bulky ligand **3b**.

Interesting results are found with the sterically more crowded ligand **3b**. From ^{31}P and ^{1}H NMR studies we obtained information about the catalytic precursor. When a 2-fold excess of **3b** was added to one equivalent of $Rh(acac)(CO)_2$, two signals were observed in a 1:1 ratio under atmospheric conditions in the ^{31}P NMR spectrum ($CDCl_3$, a singlet at δ=143.7 ppm and a doublet at δ=138.2 ppm, $J_{Rh,P}$=317 Hz). The singlet at δ=143.7 ppm occurs at exactly the same chemical shift as that of free **3b**. From the ^{31}P spectrum we could not determine if **3b** coordinates in a mono or bidentate way. To distinguish between two possible situations (figure 5) we turned to the ^{1}H spectrum. The ^{1}H NMR spectrum shows a doublet (δ = 5.12 ppm, $J_{P,H}$ = 7.4 Hz) and a triplet (δ = 5.29 ppm, $J_{P,H}$ = 5.9 Hz) in the region between 5.0 and 6.0 ppm. These signals can be assigned to the protons at C2 and C3 in respectively free **3b** and rhodium coordinated **3b**. The doublet coincides with that of free **3b**. The virtual triplet is caused by two mutually coupled phosphorus atoms via a rhodium atom. When one equivalent of **3b** was added to $Rh(acac)(CO)_2$ a doublet was observed in the ^{31}P NMR spectrum ($CDCl_3$, δ=138.7 ppm, $J_{Rh,P}$=316 Hz). The ^{1}H NMR spectrum shows a triplet in the above mentioned region (δ = 5.27 ppm, $J_{P,H}$ = 6.0 Hz). Both ^{1}H NMR spectra exhibit an additional singlet (δ = 5.13 ppm) in this region, which can be assigned to acetylacetonate. These results prompted us to assume (PP)Rh(acac) as the catalyst precursor in which **3b** coordinates in a bidentate way. It is likely that under hydroformylation conditions the catalyst has the structure $HRh(PP)(CO)_2$.

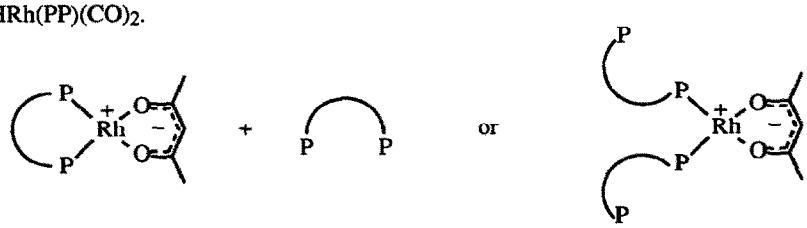


figure 5. Two possible situations when two equivalents of diphosphite ligand are added to one equivalent of $Rh(acac)(CO)_2$

At 80°C and a small excess of **3b** the iso/n ratio and enantiomeric excess (e.e.) were low (run 9). Competitive hydroformylation with $HRh(CO)_4$ cannot be excluded when a small excess of ligand is used (run 2 vs. run 9).

Table 1. Hydroformylation of Styrene with Chiral Rh-Diphosphite Catalysts.[a]

run	ligand	T (°C)	P/Rh ratio	time h	% conv. [c]	iso/n ratio[b]	% e.e[d]	config.[e]
1	none[f]	40	--	24	29.0	12.5	--	--
2	none[f]	80	--	19	97.4	1.3	--	--
3	**1a**	40	10.0	4	0.0	--	--	--
4	**2a**	40	10.0	16	3.7	5.4	7.3	R
5	**3a**	40	10.0	19	0.0	--	--	--
6	**3b**	40	10.0	5	16.2	17.8	19.9	R
7	**2a**	80	2.2	19	96.0	2.3	~0	--
8	**3a**	80	2.2	16	75.4	1.9	~0	--
9	**3b**	80	2.2	15	42.3	1.6	1.4	R
10		80	20.0	16	99.7	10.2	6.6	R
11		40	2.5	5	17.2	18.3	5.9[g]	R
12		40	2.5	24	89.7	12.6	~0	R
13		40	10.0	23	99.4	16.5	3.1	R
14		25	2.5	24	20.1	26.9	18.5	R
15		25	10.0	23	19.7	26.1	19.3	R
16		25	10.0	55	17.0	43.1	3.1[g]	R
17[h]		40	10.0	5	11.0	20.8	16.0	R
18[h]		40	10.0	24	79.5	19.2	1.2	R
19[h]		25	10.0	23	14.5	35.0	19.9	R
20[i]		40	2.5	5	75.8	24.5	8.0	R
21[i]		25	2.5	5	17.8	37.3	8.3	R

[a]All reaction were carried out with 20 mmol styrene in 30 ml of toluene under 40 bar of synthesis gas starting from $Rh(acac)(CO)_2$ with a substrate/catalyst ratio of 4000 unless otherwise stated. [b]Iso/n ratios determined by GC. [c]Conversion determined by GC. [d]Enantiomeric excesses are determined after reduction with $NaBH_4$ to 2-phenyl-1-propanol by GC equipped with a chiral cyclodextrin column. [e]Abs. configuration determined by comparison of the retention times of the two enantiomers in the mixture with the retention time of optically pure (R)-(+)-2-phenyl-1-propanol. [f]Hydroformylation with $HRh(CO)_4$. [g]The same e.e. was found after reduction with diisobutylaluminium hydride. [h]Reaction in 30 ml of triethylorthoformate. [i]Substrate/catalyst ratio of 1000.

Addition of a 20-fold excess of **3b** does not kill the activity of the catalyst. The iso/n ratio increases dramatically although little improvement in e.e. was observed (run 9 vs. run 10). Comparable results in e.e. were obtained at 40°C and a P/Rh ratio of 2.5 (run 11), but no e.e. was left at longer reaction times (run 12). A further increase in e.e. and iso/n ratio was obtained with a 10-fold excess of **3b** at moderate reaction times (run 6). As was the case

in run 12, the e.e. decreases at longer reaction times (run 13). Encouraging results were found when the reaction temperature was lowered to 25°C (run 11 vs. run 14). Even after 24 hours an e.e. of 18.5% was observed with a selectivity of 96% to the branched aldehyde. Increasing the P/Rh ratio to 10 hardly changes the e.e. and regioselectivity (run 15). When the same reaction was carried out over 55 hours the conversion did not get any higher than 17% and a low e.e. was found (run 16).

To find out if racemisation takes place during the asymmetric hydroformylation, reactions have been carried out in triethylorthoformate (runs 17-19). We expected the formation of acetals during the hydroformylation in triethylorthoformate as was reported by Stille and co-workers with their Pt/BPPM/$SnCl_3$ catalyst (BPPM stands for (N-(t-butoxycarbonyl)-(2S, 4S)-4-(diphenylphosphino)-2-[(diphenylphosphino)-methyl]pyrrolidine).[5] In contrast with the results reported by Stille and co-workers we could not detect any formation of acetals by GC, GCMS and ^1H NMR analysis. The e.e.'s determined were comparable with the e.e.'s found when the reactions were carried out in toluene (compare runs 6, 13 and 15 with resp. runs 17, 18 and 19). An e.e. of 19.9% was noted at 25°C and 23 hours reaction time. Stille and co-workers successfully formed acetals (which seemed not to be prone to racemisation) during the hydroformylation with Pt/BPPM/$SnCl_3$ catalyst probably because of the more acidic character of this system. From the results reported by Stille and co-workers it can be concluded that the rate of acetalisation exceeds the rate of racemisation. The fact that acetalisation does not occur in our system suggests that racemisation can be excluded. To find further proof for the absence of racemisation we have added the branched aldehyde of known enantiomeric excess (from run 11) with the rhodium catalyst under hydroformylation conditions. After 15 hours exactly the same e.e. was found. From these results it is obvious that the aldehydes formed during the asymmetric hydroformylation are not prone to racemisation. Within the accuracy of the experiment, we found exactly the same e.e.'s when different reducing agents were used for the reduction of 2-phenyl-1-propanal to 2-phenyl-1-propanol (runs 11 and 16). These results indicate that no racemisation takes place during the reduction step either. Since lower e.e.'s were observed at longer reaction times, we accelerated the reaction rate by means of a lower substrate/rhodium ratio of 1000 (runs 20 and 21). A fourfold increase in reaction rate was indeed observed but the e.e.'s were low even after a reaction time of 5 hours. Again a very high regioselectivity to the branched aldehyde (>97%) was found at 25°C (run 21). To the best of our knowledge the highest iso/n ratio ever reported of 62 (>98% branched aldehyde) was found by Brown and co-workers but no asymmetric induction was obtained.[19] We expect that the asymmetric induction during the hydroformylation is caused by a catalytic rhodium species in which the diphosphite coordinates in a bidentate fashion. Since the catalyst was prepared in situ we cannot exclude the formation of other catalytic active species like $HRh(CO)_4$ or a species in which diphosphite ligands coordinate in a monodentate fashion. In a typical experiment a small amount of ligand degradation was observed in the reaction mixture afterwards. Therefore the coexistence of a variety of catalytic species during the hydroformylation could be a possible explanation for the decreasing e.e.'s at longer reaction times.

CONCLUSIONS

Chiral bidentate phosphite ligands with C_2 symmetry can easily be synthesised from cheap optically active diols in moderate to good yields (32-92%). We successfully used these compounds as ligands in the rhodium catalysed asymmetric hydroformylation of styrene. With less bulky diphosphite ligands hardly any catalytic

activity and enantiomeric excess could be obtained. Enantiomeric excesses up to 20% have been obtained with the most bulky ligand under mild reaction conditions (25-40°C, 40 bar syngas pressure). The regioselectivity to the branched aldehyde is very promising (>95%). In general both the enantiomeric excesses and the regioselectivity to the branched aldehyde increases at lower reaction temperatures and an excess of bulky ligand. In conclusion, chiral bidentate phosphites can serve as a promising group of ligands in the asymmetric hydroformylation of styrene.

EXPERIMENTAL

General Information

All reaction were carried out in oven-dried glasswork using Schlenk techniques under an atmosphere of argon. Toluene and THF were distilled from sodium/benzophenone. Pyridine and triethylamine were distilled from CaH_2 and stored under an atmosphere of argon. All chemicals were purchased from Aldrich Chemical Co. For column chromatography Silica gel 60 purchased from Merck was used. Infrared (IR) spectra were recorded on a Nicolet 510 FT-IR spectrophotometer. Melting points were determined on a Gallenkamp MFB-595 melting point apparatus in open capillaries and are uncorrected. ^{31}P, ^{13}C and ^{1}H NMR spectra were obtained on a Bruker AMX 300 spectrometer. Optical rotations were measured on a Perkin Elmer 241 polarimeter. Gas chromatographic analysis were run on a Carlo Erba GC 6000 Vega Series apparatus (split/splitless injector, J&W Scientific, DB1 30m column, film thickness 3.0 μm, carrier gas: 70 kPa He, F.I.D. detector) equipped with a Hewlett Packard HP 3396 integrator. Enantiomeric excesses were measured after reduction of the aldehydes with $NaBH_4$ to the corresponding alcohols on a Carlo Erba Vega 6000 Gas Chromatograph (H.O.T. Cold on Column injector, Chrompack 50m Chiral β-Cyclodextrin column, 110°C isotherm, carrier gas: 180 kPa He, F.I.D. detector, equipped with a Shimadzu C-R 5A integrator). Hydroformylation reactions were carried out in a home-made 200 ml stainless steel autoclave. Syngas 3.0 was purchased from UCAR. The operating temperature was controlled with a WEST 3750 Temperature Controller.

Catalysis

In a typical experiment the autoclave was filled with toluene and the catalyst precursor (see Table 1) and pressurised to the appropriate initial pressure with syngas ($CO:H_2 = 1:1$). After heating the autoclave at reaction temperature, 20 mmol of the substrate and 5.0 mmol of an internal standard (decane) were brought into the autoclave. When the reaction was finished the autoclave was vented with nitrogen and opened. The reaction mixture was directly vacuum distilled to remove the catalyst and analysed with NMR and Gas Chromatography.

2,2'-Bisphenoxyphosphorus chloride (4)

This compound was prepared according to a modified literature procedure.[20] A 1 l three-necked, round-bottomed flask equipped with a 500 ml dropping funnel was filled with pyridine (600 mmol, 47.5 g) and PCl_3 (120 mmol, 16.5 g). 2,2'-Bisphenol (50 mmol, 9.31 g) was azeotropically dried with toluene (3x50 ml), dissolved in 350 ml of toluene and added dropwise to the PCl_3/pyridine solution at 0°C. When the addition was completed the reaction mixture was refluxed overnight. The formed pyridine salts were removed by filtration. The reaction mixture was concentrated at reduced pressure. The product was purified by distillation at reduced pressure (bp. 145°C, 1.0 mm Hg). Yield 18.0 g of a colourless oil (71%, purity 96-98%). The product was

stored as a 1 M solution in frozen benzene at -20°C. ^{31}P NMR ($CDCl_3$): δ 180.17 (s); ^{1}H NMR ($CDCl_3$): δ 7.54 - 7.29 (m, H, arom)

4,4',6,6'-Tetra-*t*-butyl-2,2'-bisphenol

This compound was prepared according to a modified literature procedure.[20] In a 1 l three-necked, round-bottomed flask, equipped with a gas inlet 2,4-di-*t*-butylphenol (0.48 mol, 100g) was dissolved in methanol (200 ml) Anhydrous $CuCl_2$ (3.0 mmol, 0.4 g) and tetramethylethylene diamine (TMEDA, 4.5 mmol, 0.52 g) were added. The resulting dark green solution was stirred for several days under a continuous flow of air. A white precipitate was formed during that time which was filtered off several times. After 5 days the reaction was stopped since there was hardly any reactivity left. The isolated crops were washed twice with cold methanol and dried in vacuo. Yield 57.81 g (56.4%, 0.14 mol) of a white powder. ^{1}H NMR ($CDCl_3$): δ 7.40 (d, 2 H, arom, J = 2.40 Hz), 7.12 (d, 2 H, arom, J = 2.37 Hz), 5.23 (b, 2 H, O<u>H</u>), 1.46 (s, 18 H, *o*-$C_4\underline{H}_9$), 1.34 (s, 18H, *p*-$C_4\underline{H}_9$), M.p.: 197-198°C

4,4',6,6'-Tetra-*t*-butyl-2,2'-bisphenoxyphosphorus chloride (5)

This compound was prepared according to a slightly changed literature procedure.[20] 4,4',6,6'-Tetra-*t*-butyl-2,2'-bisphenol (50.0 mmol, 20.5 g) was azeotropically dried with toluene (2x50 ml) and dissolved in toluene (100 ml). In a 1 L three-necked, round-bottomed flask, equipped with a 250 ml dropping funnel a solution of PCl_3 (55.0 mmol, 4.80 ml) and triethylamine (250 mmol, 34.8 ml) was cooled to 0°C. The 4,4',6,6'-tetra-*t*-butyl-2,2'-bisphenol/toluene solution was brought into the dropping funnel and added in 1 hour at 0°C. The reaction mixture was stirred for 1 hour at room temperature and refluxed overnight. The reaction mixture was decanted and the filtrate was filtered on a column of aluminium oxide. The residue was concentrated in vacuo and dissolved in hexane and stored at -20°C. A white precipitate was formed which was washed twice with cold hexane and dried at vacuum. Yield 8.60 g (36.2 %, 18.1 mmol). ^{31}P NMR ($CDCl_3$): δ 172.06 (s); ^{1}H NMR ($CDCl_3$): δ 7.47 (d, 2 H, arom, J = 2.28 Hz), 7.19 (d, 2 H, arom, J = 2.34 Hz), 1.49 (s, 18 H, *o*-$C_4\underline{H}_9$), 1.37 (s, 18 H, *p*-$C_4\underline{H}_9$)

1,2:5,6-Diisopropylidene-3,4-di-(2,2'-bisphenoxyphosphinoxy)-*D*-mannitol (1a)

A 100 ml three-necked, round-bottomed flask, equipped with a 250 ml dropping funnel was filled with pyridine (100 mmol, 8.1 ml) and a stock solution of **4** in benzene (12 ml, 1M). 1,2:5,6-Diisopropylidene-*D*-mannitol (**1**) (5.0 mmol, 1.31 g) prepared according to a literature procedure[21] was azeotropically dried with toluene (3x10 ml) and dissolved in toluene (50 ml). At 0°C the solution of **1** in toluene was added to the reaction mixture in 30 minutes. The reaction mixture was stirred for 3 hours at room temperature. When the reaction was complete the formed pyridine salts were filtered off. After evaporation of the solvent a white foam was obtained. The product was purified by flash column chromatography under an argon atmosphere (eluent: 40% EtOAc/5% Et_3N/hexane(v/v/v), Rf. 0.48). Yield 3.19 g (92.4%, 4.62 mmol) of a white powder. ^{31}P NMR ($CDCl_3$): δ 152.8 (s); ^{13}C NMR ($CDCl_3$): δ 149.77 (m, C(O) arom), 131.76 (s, C arom), 130.42 (s, CH arom), 129.72 (s, CH arom), 122.74 (s, CH arom), 121.98 (s, CH arom), 110.19 (s, <u>C</u>$(CH_3)_2$), 76.24 (d, CH(OP), $^{2}J_{C,P}$ = 16.60 Hz), 74.99 (s, CH), 67.20 (s, CH_2), 27.22 (s, CH_3), 25.69 (s, CH_3); ^{1}H NMR ($CDCl_3$): δ 7.46-7.02 (m, 16 H, arom), 4.64 (approx. t, 2 H, C<u>H</u>, $^{3}J_{H,H} = {}^{3}J_{P,H}$ = 8.4 Hz), 4.42 (approx. q, 2 H, C<u>H</u>, J = 6.2

Hz) 4.06 (m, 4 H, C<u>H</u>$_2$), 1.50 (s, 6 H, C<u>H</u>$_3$), 1.39 (s, 6H, C<u>H</u>$_3$); IR (KBr): 3066 (aryl-H), 2986-2937 (alkyl-H), 1067 (C-O-C) cm^{-1}, Mp.: 77-79°C, $[\alpha]_D^{22}$ = 11.0 (*c* = *1.00*, CH_2Cl_2)

(4R,5R)-α,α'-Di-(2,2'-bisphenoxyphosphinoxy)-α,α,α',α'-2,2-hexamethyl-1,3-dioxolan-4,5-dimethane (2a)

A 100 ml three-necked, round-bottomed flask, equipped with a 50 ml dropping funnel was filled with pyridine (50 mmol, 4.0 ml) and a stock solution of **4** in benzene (12 ml, 1M). α,α,α',α'-Tetramethyl-1,3-dioxolan-4,5-dimethanol (**2**) (5.0 mmol, 1.09 g) prepared according to a literature procedure[22] was azeotropically dried with toluene (3x5 ml), dissolved in toluene (25 ml) and brought into the dropping funnel. At 0°C the solution of **2** in toluene was added in 30 minutes. The reaction mixture was allowed to stir overnight at room temperature. The formed pyridine salts were filtered off. After evaporation of the solvent a white foam was obtained which was purified by flash column chromatography under an argon atmosphere (eluent: 2.5% EtOAc/toluene(v/v), Rf. 0.42). Yield 68.0% (3.40 mmol, 2.20 g) of a white solid. ^{31}P NMR ($CDCl_3$): δ 153.4 (s); ^{13}C NMR ($CDCl_3$): δ 149.41 (m, C(O) arom), 131.27 (m, C arom), 129.67 (s, C arom), 128.81 (s, CH arom), 128.68 (s, CH arom), 124.79 (s, CH arom), 122.01 (s, CH arom), 121.56 (s, CH arom), 111.52 (s, <u>C</u>(CH$_3$)$_2$), 83.79 (s, CH), 79.61 (d, C(OP), $^2J_{C,P}$ = 7.25 Hz), 27.86 (s, C(<u>C</u>H$_3$)$_2$), 27.36 (d, CH$_3$,$^3J_{C,P}$ =13.21 Hz), 25.49 (d, $^3J_{C,P}$ = 9.21 Hz), ^{1}H NMR ($CDCl_3$): δ 7.46-7.14 (m, 16 H, arom), 3.99 (s, 2 H, C<u>H</u>), 1.57 (s, 6 H, C<u>H</u>$_3$), 1.36 (s, 6 H, C<u>H</u>$_3$), 1.24 (s, 6 H, C<u>H</u>$_3$); IR (KBr): 3070 (aryl-H), 2971-2930 (alkyl-H), 1098 (C-O-C) cm^{-1}, Mp.: 93-95°C, $[\alpha]_D^{22}$ = -31.0 (*c* = *0.55*, CH_2Cl_2)

(2R,3R) 2,3-Di-(2,2'-bisphenoxyphosphinoxy) diethyl tartrate (3a)

A 100 ml three-necked, round-bottomed flask, equipped with a 100 ml dropping funnel was filled with pyridine (50 mmol, 4.1 ml) and a stock solution of **4** in benzene (12 ml, 1 M). *L*-Diethyl tartrate (**3**) (5.0 mmol, 1.03 g) was azeotropically dried with toluene (3x5 ml), dissolved in toluene (20 ml) and brought into the dropping funnel. At 0°C the solution of **3** in toluene was added in 30 minutes. The reaction mixture was allowed to stir for 3 hours at room temperature and the formed pyridine salts were filtered off. Evaporation of the solvent gave a white foam which was purified by flash column chromatography under an atmosphere of argon (eluent: 5% MeOH/CH_2Cl_2(v/v), Rf. 0.52). The product was crystallised from hexane/CH_2Cl_2 at -20°C. Yield 1.00 g (31.6%, 1.58 mmol). ^{31}P NMR ($CDCl_3$): δ 141.37 (s); ^{1}H NMR ($CDCl_3$): δ 7.55-7.06 (m, 16 H, arom), 5.18 (d, 2 H, C<u>H</u>, $J_{P,H}$ = 8.79 Hz), 4.24 (m, 4 H, C<u>H</u>$_2$), 1.25 (t, 6 H, C<u>H</u>$_3$, *J* = 7.11 Hz); IR (KBr): 3050 (aryl-H), 2983-2882 (alkyl-H), 1758 (CO) cm^{-1},Mp.: 108-110°C, $[\alpha]_D^{22}$ = -6.0 (*c* = *0.50*, CH_2Cl_2)

(2R,3R) 2,3-di-(4,4'6,6'-tetra-*t*-butyl-2,2'-bisphenoxyphosphinoxy)diethyl tartrate (3b)

In a 100 ml three-necked, round-bottomed flask, equipped with a 100 ml dropping funnel, **5** (5.0 mmol, 2.37 g) was dissolved in toluene (10 ml). An excess of triethylamine (25 mmol, 1.8 ml) was added and the solution was cooled to 0°C. *L*-Diethyl tartrate (**3**) (2.0 mmol, 0.41 g) was azeotropically dried with toluene (3x5 ml), dissolved in toluene (20 ml) and brought into the dropping funnel. At 0°C the solution of **3** in toluene was added in 30 minutes. The reaction was completed after stirring overnight. The formed triethylamine salts were filtered off. Evaporation of the solvent resulted in a white foam which was purified by flash column chromatography under an atmosphere of argon (eluent: 5% EtOAc/Hexane(v/v), Rf. 0.27). Yield 1.40 g (64.7%, 1.29 mmol) of a white powder. ^{31}P NMR ($CDCl_3$): δ 143.68 (s); ^{13}C NMR ($CDCl_3$): δ 168.09 (s,

C(O)O), 146.99 (s, C arom) 146.67 (s, C' arom), 146.29 (d, C(O) arom, $^2J_{PC}$ = 7.5 Hz), 145.90 (d, C(O)' arom, J_{PC} = 7.5 Hz), 140.99 (s, C arom), 140.83 (s, C' arom), 133.65 (s, C arom), 133.09 (s, C' arom), 127.25 (s, CH arom), 126.96 (s, CH' arom), 124.73 (s, CH arom), 124.60 (s, CH' arom), 74.68 (s, CH), 62.22 (s, OCH_2), 35.95 (s, *o*-$\underline{C}(CH_3)_3$), 35.86 (s, *o*-$\underline{C}(CH_3)_3$), 35.20 (s, *p*-$\underline{C}(CH_3)_3$), 35.16 (s, *p*-$\underline{C}(CH_3)_3$), 32.11 (s, *p*-$C(\underline{C}H_3)_3$), 31.78 (s,*o*-$C(\underline{C}H_3)_3$), 31.69 (s, *o*-$C(\underline{C}H_3)_3$), 14.49 (s, $OCH_2\underline{C}H_3$); ^{1}H NMR ($CDCl_3$): δ 7.40 (dd, 4 H, arom, J = 2.40 Hz), 7.14 (dd, 4 H, arom, J = 2.49 Hz), 5.12 (d, 2 H, $C\underline{H}$, $J_{P,H}$ = 7.38 Hz), 4.22 (m, 4 H, $C\underline{H}_2$), 1.43 (s, 18 H, *o*-$C_4\underline{H}_9$), 1.40 (s, 18 H, *o*-$C_4\underline{H}_9$), 1.34 (s, 36 H, *p*-$C_4\underline{H}_9$), 1.02 (t, 6 H, $C\underline{H}_3$, J = 7.17 Hz); IR (KBr): 3053 (aryl-H), 2964-2891 (alkyl-H), 1762 (CO) cm^{-1}, Mp.:107-109°C, $[\alpha]_D^{22}$ =11.1 (*c* = *1.00*, CH_2Cl_2)

Acknowledgement. We thank G. U-A-Sai for his technical assistance by the determination of the enantiomeric excesses. We thank W. Dinsbach and S.L. Oei for their experimental assistance. We thank Innovation Oriented Research Programme (IOP) for their financial support of this research.

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