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Enantioselective Catalysis, 85 [1]

Optically Active Expanded Chelate Phosphines Derived from 1,ω-Bis(dichlorophosphino)alkanes

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Abstract: Optically active expanded chelate phosphines were synthesised by reaction of bromotolyl, bromoxylyl and bromodiphenylmethane derivatives with 1,ω-bis(dichlorophosphino)alkanes. The bromotolyl, bromoxylyl and bromodiphenylmethane ethers were obtained from the corresponding bromo(bromomethyl)arenes and the optically active alcohol (-)-borneol.

Introduction

Most of the optically active chelate phosphines used in enantioselective transition metal catalysts, such as diop[2,3], prophos[4], chiraphos[5], bppm[6], bppfa[7], norphos[8] or binap[9] consist of a chiral skeleton bearing two diphenylphosphine groups. The chiral information is transfered via the arrrangement of the phenyl rings of the diphenylphosphine groups to the metal centre, where the catalysis occurs. Due to the limited size of the diphenylphosphine groups, long range effects are not possible with these conventional ligands, although they are extremely effective in a variety of reaction types[10,11].

The concept of the expanded phosphines represents a new approach to expand optically active phosphines. The expanded phosphines should contain a P-P chelate skeleton and different layers attached to the P atoms. The P-P backbone should permit a strongly chelating coordination to the central metal atom of a catalyst. The layers should be made up of nonchiral groups (constructive units) and of chiral groups (functional units), respectively. Using branching elements, the following layer will consist of two times the number of units of the preceding layer. By multiple repetition of such layers an expansion will result, giving space-filling dendrimer ligands[12]. The final layer, the "edge" of the molecules, may easily be built up from enantiomerically pure compounds. In this way, it should be possible to chirally shape the surroundings of the P atoms of a P-P skeleton in a wide range[13,14]. After coordination in a catalyst, an influence on the optical induction in enantioselective reactions is expected.

In the present paper the syntheses and characterisation of the expanded ligands **4** - **6** is reported, constructed according to the concept outlined above. The strongly binding backbones of the ligands are derived from 1,ω-bis(dichlorophosphino)alkanes **1** - **3**[15-17], allowing the formation of four-, five- and seven-membered chelate rings[13]. The strategy for the synthesis of the expanded phosphines is to prepare the substituent-precursors first, starting from the outside and moving to the inside. Then, the two-membered and three-membered substituents are connected to the P atoms of the chelate skeleton.

Preparation of the expanded phosphines

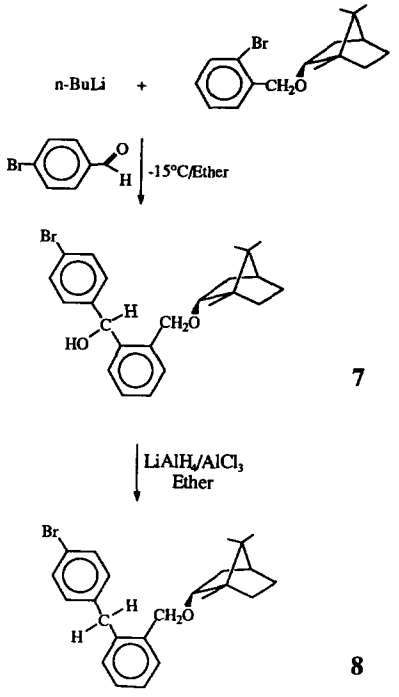
The syntheses start with the optically active alcohol (-)-borneol, forming the end group of the substituents. It is connected to the benzylic positions of 2-bromotoluene, 4-bromotoluene and 5-bromo-1,3-xylene, respectively, by reacting its Na derivative with the benzylic bromo substituents of 2-bromobenzylbromide, 4-bromobenzylbromide and 5-bromo-1,3-di(bromomethyl)benzene, obtained by NBS-bromination of 2-bromotoluene, 4-bromotoluene and 5-bromo-1,3-xylene[18,19]. In this nucleophilic substitution two-membered substituent-precursors are accessible, being arylbromides. One of them, (-)-2-(borneoxymethyl)bromobenzene is shown in Scheme 1.

Three-membered substituent-precursors can be built up starting from the two-membered substituent-precursors by a halide-metal exchange with n-BuLi. The lithiated species are reacted with bromobenzaldehydes. The resulting benzhydrol derivatives can be reduced to the corresponding diphenylmethanes. The preparation of the three-membered substituent-precursor **8** is shown in Scheme 1. Treatment of (-)-2-(borneoxymethyl)bromobenzene with n-BuLi gives the lithiated species, which reacts with 4-bromobenzaldehyde to give the benzhydrol derivative **7**. With a mixture of $LiAlH_4$ and $AlCl_3$ this secondary alcohol is reduced to the corresponding diphenylmethane **8**.

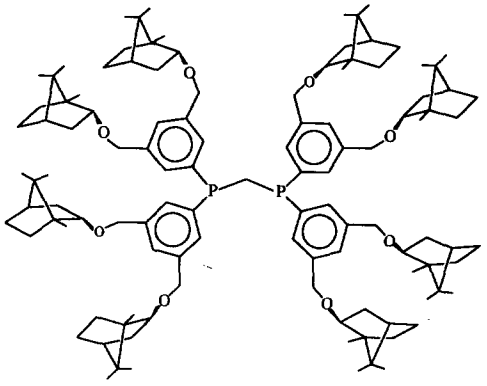
The bromo substituents at the arene can be used to connect the prefabricated two-membered and three-membered substituent-precursors to the P atoms of the chelate skeleton, because they are inert with respect to the preceding nucleophilic substitution, but reactive with respect to the subsequent halide-metal exchange with n-BuLi. This halide-metal exchange gives the lithiated species which ultimately react with the 1,ω-bis(dichlorophosphino)alkanes **1** - **3**, yielding the final expanded phosphines **4** - **6** (Scheme 2). The expanded phosphine **4b** is shown in Scheme 3.

The two-membered and three-membered substituent-precursors are distillable liquids. The two-layer phosphines of type **a** and **b** are solids, whereas the three-layer phosphines of type **c** and **d** are oils.

The EI/FD mass spectra of the benzhydrols, the diphenylmethanes and the expanded ligands **4** - **6** contain the molecular ions. In the ^{1}H-NMR spectra, the benzylic methylene protons form AB systems, due to the neighborhood of the bornyl groups. However, the



Scheme 1



4b

Scheme 3

Ar—Br
1. n-BuLi
2. Cl2P
PCl2
1
Ar—Br
1. n-BuLi
2. Cl2P
PCl2
2
Ar—Br
1. n-BuLi
2. Cl2P
PCl2
3
Ar
P
Ar
Ar
P
Ar
4
Ar
P
Ar
Ar
P
Ar
5
Ar
P
Ar
Ar
P
Ar
6
a
b
c
d
Ar =
CH2O
CH2
H2C
OH2C

Scheme 2

methylene bridges of the diphenylmethane system appear as singlets. The ^{31}P-NMR spectra show singlets for all the ligands **4** - **6**.

To determine the size of the expanded phosphines, molecular modeling of a P-substituent was carried out (PC Model 4.0, Serena Software, Box 3076, Blomington, IN 47402-3076). Excluding distortions, the maximum distance between the P atom and the most distant H atom of a substituent is 5.8 Å for the parent ligand diphos-(2), 11.9 Å for the two-layer ligand **4b**, and 17.3 Å for the three-layer ligand **5d**.

Enantioselective hydrogenation of (α)-N-acetamidocinnamic acid

The Rh catalysed hydrogenation of (α)-N-acetamidocinnamic acid is a well known test reaction for new optically active phosphine ligands in enantioselective catalysis. *In situ* catalysts were used consisting of $[Rh(cod)Cl]_2$ and the optically active phosphines **4a**, **4b**, and **6a**, respectively. All experiments were carried out at 20 bar H_2 pressure in the solvent methanol. The reaction time was 20 hours and the Rh:substrate ratio was 1:50. For work up and determination of the chemical yield and the enantiomeric excess, the methods described in the literature were used[20, 21].

In all cases, 100% hydrogenation was achieved. However, the optical inductions were disappointingly low [**4a**: 5.2 % ee (R); **4b**: 2.0 % ee (R); **6a**: 2.3 % ee (R)]. The reason for this may be, that the expanded ligands **4a**, **4b**, and **6a**, although containing "a lot of chirality", can adopt a variety of different conformations. Thus, in future syntheses, more rigidity will have to be introduced into the expanded systems.

A positive point: Expansion of the phosphines could have been associated with a drop in hydrogenation rate. Fortunately, this is not the case. Kinetic studies[22] showed, that the reaction rates in the Rh catalysed hydrogenation of (α)-N-acetamidocinnamic acid with the two-layer phosphines are in the same range as with their parent ligand diphos-(2), $Ph_2PCH_2CH_2PPh_2$.

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Experimental

^{1}H-NMR and ^{31}P-NMR spectra were recorded on a Bruker WM 250 spectrometer and were referenced to internal TMS and external H_3PO_4, respectively. FD-mass spectra were recorded on a Finnigan MAT 95 spectrometer, for EI-mass spectra a Varian MAT 311 A spectrometer was used. The 1,ω-bis(dichlorophosphino)alkanes, 1,1-bis(dichlorophosphino)methane **1**[15], 1,2-bis(dichlorophosphino)ethane **2**[16], 1,4-bis(dichlorophosphino)butane **3**[17], and the two-membered substituent-precursors derived from 2-bromobenzylbromide, 4-bromobenzylbromide, 5-bromo-1,3-di(bromomethyl)benzene and (-)-borneol[13,14] were prepared as described in the literature.

Preparation of the Benzhydrols: General Method

(-)-2-Borneoxymethyl-1-bromobenzene or (-)-4-borneoxymethyl-1-bromobenzene (5 g, 15.5 mmol) were dissolved in ether under nitrogen and cooled to -15°C. Then, n-BuLi (9.7 ml, 15.5 mmol, 1.6 mol/l in hexane) was added and the solution stirred for 30 min. After addition of a solution of 4-bromobenzaldehyde (2.86 g, 15.5 mmol) in 20 ml of ether, the reaction mixture was refluxed for 24 h. After cooling, the solution was hydrolysed with 50 ml of water. The ether layer was washed with water to neutrality, dried and evaporated. The oily residue was distilled bulb to bulb under reduced pressure using a Kugelrohr.

(-)-α-(2-Borneoxymethyl)phenyl-4'-bromobenzylalcohol (7)

Yield: 65%; b.p.: 150°C/10^{-3} Torr; IR (Film): 3600 - 3100, 2980, 2960, 2860, 1600, 1580, 760 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.70 - 7.11 (m, 8H, Ar-H), 5.99 - 5.95 (m, 1H, methin-H), 4.50, 4.39 (AB, J_{AB} = 11.0, 2H, Ar-CH_2), 4.36 - 4.25 (m, 1H, OH), 3.76 - 3.69 (m, 1H, CH-O), 2.19 - 0.80 (m, 16H, bornyl-H); MS (EI): m/z 428/430 M^+; $[\alpha]_D^{25}$ = - 26.8 (c = 1, CH_2Cl_2). Anal. calcd. for $C_{24}H_{29}BrO_2$ (429.4): C, 67.13; H, 6.81; Br, 18.61; found, C, 67.43; H, 6.78; Br, 18.43.

(-)-α-(4-Borneoxymethyl)phenyl-4'-bromobenzylalcohol (8)

Yield: 52%; b.p.: 200°C/10^{-3} Torr; IR (Film): 3100, 2980, 2960, 2860, 1600, 1580, 760 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.45 - 7.22 (2AA'BB', 8H, Ar-H), 5.77 (d, J = 3.0, 1H, methin-H), 4.55, 4.42 (AB, J_{AB} = 12.3, 2H, Ar-CH_2), 3.71 - 3.65 (m, 1H, CH-O), 2.28 (d, J = 3.0, 1H, OH), 2.24 - 0.80 (m, 16H, bornyl-H); MS (EI): m/z 428/430 M^+; $[\alpha]_D^{25}$ = - 31.7 (c = 1, CH_2Cl_2). Anal. calcd. for $C_{24}H_{29}BrO_2$ (429.4): C, 67.13; H, 6.81; Br, 18.61; found., C, 67.11; H, 6.82; Br, 18.58.

Preparation of the Diphenylmethanes: General Method

7 or **8** (2.71 g, 6.31 mmol) were dissolved in 25 ml of ether. This solution was added dropwise to a slurry of $AlCl_3$ (1.1 g, 8.3 mmol) and $LiAlH_4$ (0.42 g, 1.4 mmol) in 50 ml of ether and refluxed for 2 h. After cooling, the excess of reducing agent was decomposed with 5 ml of ethyl acetate. Then the solution was washed with 10% H_2SO_4, 1N NaOH and water. The organic layer was dried over Na_2SO_4 and evaporated. The oily residue was distilled bulb to bulb under reduced pressure using a Kugelrohr.

(-)-2-Borneoxymethyl-4'-bromodiphenylmethane (9)

Yield: 81%; b.p.: 140°C/10^{-3} Torr; IR (Film): 2970, 2940, 2860, 1600, 1580, 760 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.48 - 6.97 (m, 8H, Ar-H), 4.46, 4.35 (AB, J_{AB} = 11.8, 2H, Ar-CH_2), 4.00 (s, 2H, Ar-CH_2-Ar), 3.66 - 3.60 (m, 1H, CH-O), 2.28 - 0.81 (m, 16H, bornyl-H); MS (EI): m/z 412/414 M^+; $[\alpha]_D^{25}$ = - 33.4 (c = 1, CH_2Cl_2). Anal. calcd. for $C_{24}H_{29}BrO$ (413.4): C, 69.73; H, 7.07; Br, 19.32; found, C, 69.85; H, 6.76; Br, 19.18.

(-)-4-Borneoxymethyl-4'-bromodiphenylmethane (10)

Yield: 70%; b.p.: 150°C/10^{-3} Torr; IR (Film): 2980, 2960, 2860, 1600, 1580, 800 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.44, 7.40, 7.06, 7.02, 7.28, 7.14, 7.13, 7.09 (2AA'BB', 8H, Ar-H), 4.53, 4.41 (AB, J_{AB} = 12.1, 2H, Ar-CH_2), 3.90 (s, 2H, Ar-CH_2-Ar), 3.67 - 3.65 (m, 1H, CH-O),

2.16 - 0.80 (m, 16H, bornyl-H); MS (EI): m/z 412/414 M^+; $[\alpha]_D^{25}$ = - 29.3 (c = 1, CH_2Cl_2). Anal. calcd. for $C_{24}H_{29}BrO$ (413.4): C, 69.73; H, 7.07; Br, 19.32; found, C, 69.75; H, 6.98; Br, 19.20.

Preparation of the Two-layer Phosphines: General Method

(-)-2-Borneoxymethyl-1-bromobenzene, (-)-4-borneoxymethyl-1-bromobenzene or (-)-5-bromo-1,3-di(borneoxymethyl)benzene (15.5 mmol) were dissolved in 30 ml of absolute THF and cooled to -78°C. Then, n-BuLi (9.7 ml, 15.5 mmol, 1.6 mol/l in hexane) was added. After 30 min of stirring, the respective 1,ω-bis(dichlorophosphino)alkane **1** - **3** (3.86 mmol) was added. The reaction mixture was stirred for another 12 h in the spontaneously warming bath. Then, the solution was evaporated to dryness and the residue dissolved in 40 ml of ether. This solution was hydrolysed with 5 ml of water. The ether layer was separated and dried. After filtration the solvent was evaporated, leaving a colorless, oily product. Treatment with ethanol gave a colorless precipitate. This was filtered off, washed with ethanol and dried under reduced pressure.

(-)-1,1-Bis[di(2'-borneoxymethylphenyl)phosphino]methane (4a)

Yield: 52%; m.p.: 87.5°; IR (KBr): 2970, 2960, 2850, 1440, 1370, 1350 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.55 - 7.50 (m, 4H, Ar-H), 7.35 - 7.16 (m, 12H, Ar-H), 4.64 - 4.37 (4AB, 8H, Ar-CH_2), 3.56 - 3.49 (m, 4H, CH-O), 2.60 - 2.59 (m, 2H, P-CH_2-P), 2.08 - 0.80 (m, 64H, bornyl-H); ^{31}P-NMR ($CDCl_3/CHCl_3$ = 1:1): δ - 46.2 (s); MS (FD/acetone): m/z 1048.7 M^+; $[\alpha]_D^{25}$ = - 48.0 (c = 1, CH_2Cl_2). Anal. calcd. for $C_{69}H_{94}O_4P_2$ (1049.5): C, 78.96; H, 9.03; found, C, 78.54; H, 8.72.

(-)-1,1-Bis{di[3',5'-di(borneoxymethyl)phenyl]phosphino}methane (4b)

Yield: 48%; m.p.: 76°; IR (KBr): 2970, 2960, 2850, 1445, 1360, 1340 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.30 - 7.23 (m, 12H, Ar-H), 4.49, 4.37 (AB, J_{AB} = 12.5, 16H, Ar-CH_2), 3.65 - 3.62 (m, 8H, CH-O), 2.09 - 0.80 (m, 130H, bornyl-H, P-CH_2-P); ^{31}P-NMR ($CDCl_3/CHCl_3$ = 1:1): δ - 20.1 (s); MS (FD/acetone): m/z 1714.5 M^+; $[\alpha]_D^{25}$ = - 63.3 (c = 1, CH_2Cl_2). Anal. calcd. for $C_{113}H_{166}O_8P_2$ (1714.5): C, 79.16; H, 9.76; found, C, 79.31; H, 9.44.

(-)-1,4-Bis[di(2'-borneoxymethylphenyl)phosphino]butane (6a)

Yield: 55%; m.p.: 55°; IR (KBr): 2970, 2960, 2850, 1440, 1370, 1350 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.51 - 7.15 (m, 16H, Ar-H), 4.86 - 4.38 (4AB, 8H, Ar-CH_2), 3.68 - 3.58 (m, 4H, CH-O), 2.16 - 0.78 (m, 72H, bornyl-H, P-$(CH_2)_4$-P); ^{31}P-NMR ($CDCl_3/CHCl_3$ = 1:1): δ - 40.9 (s); MS (FD/acetone): m/z 1091.5 M^+; $[\alpha]_D^{25}$ = - 47.5 (c = 1, CH_2Cl_2). Anal. calcd. for $C_{72}H_{100}O_4P_2$ (1091.5): C, 79.21; H, 9.23; found, C, 78.93; H, 9.29.

Preparation of the Three-layer Phosphines: General Method

9 or **10** (2 g, 4.84 mmol) were dissolved in 30 ml of ether and cooled to -15°C. Then, n-BuLi (3.03 ml, 4.84 mmol, 1.6 mol/l in hexane) was added. After 30 min of stirring, 1,2-bis(dichlorophosphino)ethane **2** (280.0 mg, 0.20 ml, 1.21 mmol) was added and the reaction mixture stirred for another 12 h in the spontaneously warming bath. For work up, the solution

was hydrolysed with 5 ml of water, the organic layer separated and dried over Na_2SO_4. After filtration the solution was evaporated to dryness. The oily residue was dissolved in the minimum quantity of ethanol and cooled to 8°C. After 6 h a colorless oil was obtained. The ethanol was decanted and the oil dried under reduced pressure.

(-)-1,2-Bis[di(2"-borneoxymethylphenyl-4'-benzyl)phosphino]ethane (5c)
Yield: 45%; IR (Film): 2960, 2940, 2850, 1440, 1370, 1350 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.48 - 7.12 (m, 32H, Ar-H), 4.49, 4.39 (AB, J_{AB} = 11.0, 8H, Ar-CH_2), 4.01 (s, 8H, Ar-CH_2-Ar), 3.75 - 3.67 (m, 4H, CH-O), 2.15 - 0.71 (m, 68H, bornyl-H, P-$(CH_2)_2$-P); ^{31}P-NMR ($CDCl_3/CHCl_3$ = 1:1): δ - 13.1 (s); MS (FD/acetone): m/z 1423.9 M^+; $[\alpha]_D^{25}$ = - 27.6 (c = 1, CH_2Cl_2). Anal. calcd. for $C_{98}H_{120}O_4P_2$ (1424.0): C, 82.66; H, 8.49; found, C, 81.75; H, 7.65.

(-)-1,2-Bis[di(4"-borneoxymethylphenyl-4'-benzyl)phosphino]ethane (5d)
Yield: 55%; IR (Film): 2970, 2960, 2850, 1440, 1370, 1350 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.42 - 7.02 (m, 32H, Ar-H), 4.52, 4.41 (AB, J_{AB} = 12.0, 8H, Ar-CH_2), 3.91 (s, 8H, Ar-CH_2-Ar), 3.70 - 3.65 (m, 4H, CH-O), 2.17 - 0.80 (m, 68H, bornyl-H, P-$(CH_2)_2$-P); ^{31}P-NMR ($CDCl_3/CHCl_3$ = 1:1): δ - 13.2 (s); MS (FD/acetone): m/z 1423.9 M^+; $[\alpha]_D^{25}$ = - 35.2 (c = 1, CH_2Cl_2). Anal. calcd. for $C_{98}H_{120}O_4P_2$ (1424.0): C, 82.66; H, 8.49; found, C, 81.68; H, 7.88.

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