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Carbohydrate-substituted phosphines as new ligands for two-phase catalysis – synthesis and application

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Abstract

The synthesis and catalytic application of a new class of polar hydrophilic phosphines for two-phase catalysis is described in full detail. Contrary to the well-known sulfonated phosphines the hydrophilic character of the ligands is attributed to a neutral carbohydrate moiety. Two general routes for the synthesis of monosaccharide substituted triarylphosphines are presented. In the first procedure protected halopyranoses and OH-substituted triphenylphosphines were combined under phase transfer conditions to generate carbohydrate-substituted phosphines. In a second more efficient protocol, the palladium-catalyzed coupling of suitable haloaryl glycosides with diphenylphosphine constitutes a new access to these ligands. The properties of the ligands in terms of solubility, surfactant activity, and partition between two non-miscible phases are discussed. In addition, superior catalytic performance compared to ionic hydrophilic ligands was demonstrated for important C–C coupling reactions such as the Suzuki, Heck, and hydroformylation reactions.

Keywords: Two-phase catalysis; Glycosides; Phosphines; Suzuki reaction; Heck reaction; Hydroformylation

1. Introduction

Two-phase catalysis is probably the most elegant method to overcome the two basic problems of homogeneous catalysis: separation and recycling of the catalyst. In general this technique uses a homogeneous catalyst dissolved in a hydrophilic solvent, e.g. water, while starting materials as well as products are mainly dissolved in a second organic phase. Due to the low-cost and simple catalyst separation and the exploitation of the advantages of homogeneous catalysis (e.g. mild reaction conditions, chemically defined catalysts, tailoring catalysts) versus heterogeneous catalysis (e.g. easy catalyst separation) aqueous/organic systems as well as other biphasic or phase transfer systems have already been implemented in a number of industrial processes. Most important in terms of production volume are the shell higher olefine process (SHOP) [1,2], and the Ruhrchemie/Rhône–Poulenc process [3,4] for the hydroformylation of propene. Besides the Kuraray process [5] for butadiene telomerization, key steps for the production of vitamin E building blocks (Rhône–Poulenc) [6], and propylene dimerization (IFP) [7,8] are industrially applied. Surprisingly, despite the industrial importance the investigation of liquid/liquid biphasic variants has only recently become one of the most active areas of academic research in homogeneous catalysis [9–11].

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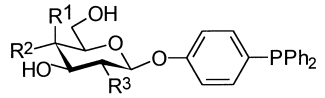
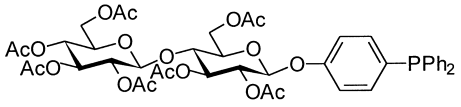
In order to apply two-phase catalysis to organic synthesis the catalyst must be preferentially soluble in a polar phase of a biphasic mixture. Here hydrophilic ligands (usually phosphines) can immobilize the catalyst in the polar phase. Numerous phosphine ligands have been introduced in the literature in recent years, but almost all use ionic groups for the purpose of hydrophilic solubility [9–11]. Phosphine ligands with a neutral polar group have been used to a much lesser extent. Obviously, carbohydrates constitute an interesting class of non-ionic hydrophilic groups which are available as chiral, renewable resources. To the best of our knowledge only three examples of phosphine ligands bearing a non-protected carbohydrate moiety (Fig. 1) have been described in the literature. In **1**, the hydroxy group of the carbohydrate is alkylated with a diphenylphosphinopropyl moiety [12], while **2a** and **b** contain β-cyclodextrin as a sugar component [13,14].

Clearly, carbohydrate-substituted phosphines remain to be explored in terms of scope and generality. In this respect we have shown that 1-*O*-glycosides of hydroxytriarylphosphines are available in general by a two-phase glycosidation reaction [15] (see Fig. 2).

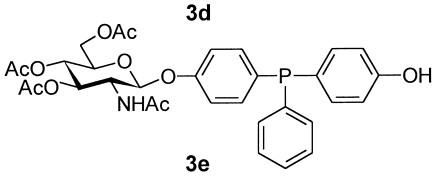
In this paper we present, for the first time, full details on the synthesis of these ligands and their catalytic properties for Heck and Suzuki reactions. Furthermore, our continuing interest in these ligands allowed us to develop an alternative synthetic protocol to this class of compounds and to explore further catalytic behavior, e.g. for the hydroformylation of 1-octene.



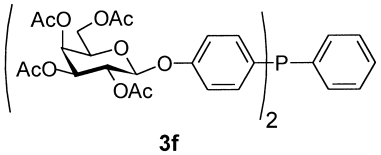
3a R^1 = H, R^2 = OH, R^3 = NHAc
3b R^1 = OH, R^2 = H, R^3 = OH
3c R^1 = H, R^2 = OH, R^3 = OH



3d



3e



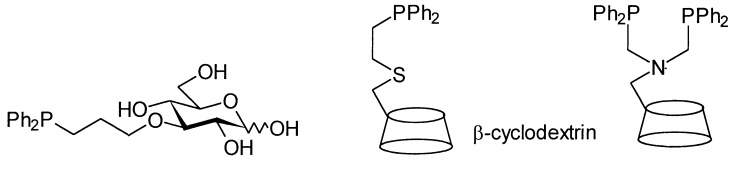
3f

Fig. 2. Prepared carbohydrate-substituted triphenylphosphines.

2. Experimental

All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. All solvents were dried and deoxygenated by distillation under argon when necessary. Chemicals were purchased from Fluka or Aldrich and used without further purification. The syngas (CO/H_2 50/50, purity 99.98) used in the hydroformylation experiments was purchased from Messer Griesheim. Compounds **4a–c** [16], **5** [17–19], and **7** [21,22] were prepared according to the literature.

NMR measurements were done on JEOL NMR 270, JEOL NMR 400 or Bruker am 360. The key to the NMR data is: s, singlet; d, doublet; t, triplet; quart, quartet; quin, quintet; m, multiplet; br, broad. The



1 **2a** **2b**

Fig. 1. Ligands with carbohydrate moieties.

chemical shifts are given in ppm. IR data were collected on a Perkin Elmer 1600 FTIR spectrometer. Mass spectroscopy was done on a MAT 90 mass spectrometer (Finnigan MAT, Bremen, Germany). The elementary analysis and rhodium analysis were done by the Mikroanalytisches Labor der Technischen Universität München. The reaction product distribution in the Heck and hydroformylation reactions were analyzed by gas chromatography on a Hewlett Packard 6890 series GC system equipped with a HP 5 column 30 m×0.32 mm×0.25 μm and FID detector.

2.1. *Synthesis of the glycosidated ligands* **3a–e**

Compounds **5a** or **b** [16] (1 equiv) and TBAHS (tetrabutylammoniumhydrogensulfate) were dissolved in CH_2Cl_2 (ca. 0.4 M solution) and treated with the same volume of 1 M NaOH solution. After 5 min **4a–c** [17–19] (5 equiv) was added and after 30 min the mixture was diluted with the eight-fold amount of ethyl acetate. The organic layer was washed with 1 M NaOH solution (2×), with water (2×), and with saturated brine (2×). After separation the organic phase was dried over $MgSO_4$ and the solvent was evaporated. In the cases of **3d** and **e** the residue was purified by column chromatography (silica gel 60) using ethyl acetate/hexane (1:2, v/v) as eluent. In case of **3a–c** the residue was taken up in methanol and treated with sodium methanolate in methanol (1 M, 100 μl). After 30 min the mixture was diluted with methanol (20 ml), and the solution was neutralized with an acidic ion exchange (Amberlyst 15). The ion exchange resin was filtered off, the solvent evaporated, and the residue purified by column chromatography (silica gel 60) ($CHCl_3$/methanol/hexane, 6:1:1, v/v/v).

2.1.1. *1-O-[4-(diphenylphosphino)phenyl]-2-acetamido-2-desoxy-β-D-glucopyranoside* **3a**

C,H,N-analysis calculated for $C_{26}H_{28}NO_6P$ (1.5 H_2O: $C_{61.41}$, $H_{6.14}$, $N_{2.75}$; found: $C_{61.48}$, $H_{6.06}$, $N_{2.67}$; ^{1}H-NMR (360 MHz, [D_6]DMSO, 25°C): δ=7.79 (d, 8.8 Hz, 1H), 7.37 (m, 6H), 7.18 (m, 6H), 6.99 (d, 8.1 Hz, 2H), 5.09 (dd, 5.2 Hz, 13.2 Hz, 2H), 5.00 (d, 8.4 Hz, 1H), 4.59 (m, 1H), 3.68 (m, 2H), 3.37 (s, 3H), 3.18 (m, 1H), 1.79 (s, 3H); ^{13}C{^{1}H}-NMR (90 MHz, [D_6]DMSO, 25°C): δ=169.3 (s), 158.2 (s), 137.2 (d, 11.1 Hz), 135.1 (d, 21.2 Hz), 131.5 (d, 10.4 Hz), 132.9 (d, 19.0 Hz), 128.7 (s), 128.7 (d, 11.3 Hz), 116.6 (d, 8.0 Hz), 98.6 (s), 77.2 (s), 74.0 (s), 70.3 (s), 60.7 (s), 55.4 (s), 23.0 (s); ^{31}P{^{1}H}-NMR (101 MHz, [D_6]DMSO, 25°C): δ=−2.7; IR (cm^{-1}, KBr): ν=3275, 3069, 2925, 1653, 1558, 1540, 1496, 1435, 1374, 1237, 1077, 825, 743, 696.

2.1.2. *1-O-[4-(diphenylphosphino)phenyl]-β-D-galactopyranoside* **3b**

^{1}H-NMR (270 MHz, [D_6]DMSO, 25°C): δ=7.6 (m, 12H), 7.20 (d, 8.2 Hz, 2H), 5.18 (m, 1H), 4.85 (m, 2H), 4.62 (m, 1H), 4.52 (m, 1H), 3.8 (m, 1H), 3.7 (m, 1H), 3.5 (m, 4H); ^{13}C{^{1}H}-NMR (68 MHz, [D_6]DMSO, 25°C): δ=158.6 (s), 137.5 (d, 11.1 Hz), 135.2 (d, 21.3 Hz), 133.2 (d, 20.4 Hz), 131.7 (d, 13.0 Hz), 128.9 (d, 7.1 Hz), 128.9 (s), 116.8 (d, 8.2 Hz), 100.9 (s), 75.8 (s), 73.5 (s), 70.4 (s), 68.3 (s), 60.6 (s); ^{31}P{^{1}H}-NMR (109 MHz, [D_6]DMSO, 25°C): δ=−2.9; IR (cm^{-1}, KBr): ν=3372, 2922, 1591, 1496, 1433, 1400, 1232, 1181, 1072, 828, 743, 696; FAB-MS: *m/z*: 391 [M^+-H_2O-CH_3O], 279, 167, 149, 136.

2.1.3. *1-O-[4-(diphenylphosphino)phenyl]-β-D-glucopyranoside* **3c**

C,H-analysis calculated for $C_{24}H_{25}O_6P$:$C_{65.45}$, $H_{5.72}$. found: $C_{65.41}$, $H_{5.84}$; ^{1}H-NMR (360 MHz, [D_6]DMSO, 25°C): δ=7.44 (m, 6H), 7.28 (m, 6H), 7.09 (d, 8.6 Hz, 2H), 5.41 (s(br), 1H), 5.20 (s(br), 1H), 5.14 (s(br), 1H), 4.94 (d, 7.1 Hz, 1H), 4.61 (s(br), 1H), 3.69 (d(br), 11.6 Hz), 3.47 (dd, 5.6 Hz, 11.7 Hz, 1H), 3.40−3.10 (m, 4H); ^{13}C{^{1}H}-NMR (90 MHz, [D_6]-DMSO, 25°C): δ=158.3 (s), 137.2 (d, 11.3 Hz), 135.9 (d, 21.2 Hz), 132.9 (d, 19.3 Hz), 128.7 (s), 128.6 (d, 6.7 Hz), 128.3 (d, 9.3 Hz), 116.6 (d, 8.1 Hz), 100.1 (s), 77.1 (s), 76.6 (s), 73.2 (s), 69.7 (s), 60.7 (s); ^{31}P{^{1}H}-NMR (101 MHz, [D_6]DMSO, 25°C,): δ=−2.9; IR (cm^{-1}, KBr): ν=3374, 2923, 1592, 1495, 1433, 1400, 1235, 1181, 1072, 828, 743, 696; FAB-MS: *m/z*: 441 [M+H^+], 278, 221, 154, 147, 136.

2.1.4. *1-O-[4-(diphenylphosphino)phenyl]-2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyl-2,3,6-tri-O-acetyl-β-D-glucopyranosid* **3d**

^{1}H-NMR (360 MHz, $CDCl_3$, 25°C): 7.32–7.19 (m, 12H), 6.91 (dd, 1.0 Hz, 8.8 Hz, 2H), 5.26–5.01 (m, 6H), 4.91 (dd, 7.9 Hz, 9.2 Hz, 1H), 4.49 (d, 7.9, 1H), 4.47 (dd, 1H), 4.36 (dd, 4.3 Hz, 12.5 Hz, 1H), 4.11 (dd, 5.8 Hz, 11.9 Hz, 1H), 4.03 (dd, 2.3 Hz, 12.6 Hz, 1H), 3.83 (t, 9.9 Hz, 1 H), 3.74 (m, 2H), 3.63 (ddd,

1H), 2.06 (s, 3H), 2.02 (s, 6H), 2.01 (s, 3H), 2.00 (s, 3H), 1.98 (s, 3H), 1.96 (s, 3H); $^{13}C\{^1H\}$-NMR (90 MHz, $CDCl_3$, 25°C): δ=170.1 (s), 169.7 (s), 169.5 (s), 169.2 (s), 168.9 (s), 157.3 (s), 137.3 (d, 10.7 Hz), 135.4 (d, 20.9 Hz), 133.4 (d, 19.5 Hz), 130.8 (d, 9.9 Hz), 128.6 (s), 128.4 (d, 6.5 Hz), 116.8 (d, 7.7 Hz), 100.8 (s), 98.4 (s), 77.2 (s), 76.9 (s), 76.3 (s), 72.8 (s), 72.8 (s), 72.4 (s), 71.9 (s), 71.5 (s), 71.2 (s), 67.7 (s), 20.7 (s), 20.6 (s), 20.5 (s); $^{31}P\{^1H\}$-NMR (101 MHz, $CDCl_3$, 25°C): δ=−6.2; FAB-MS: *m/z*: 897 [M+H$^+$], 619, 549, 331, 279, 169, 109.

2.1.5. *1-O-[4-(4-hydroxyphenyl-phenylphosphino)-phenyl]-2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosid* **3e**

^1H-NMR (360 MHz, $CDCl_3$, 25°C): δ=7.28−7.08 (m, 9H), 6.89 (d, 8.8 Hz, 2H), 6.79 (d, 8.5 Hz, 2H), 6.07 (dd, 5.3 Hz, 8.7 Hz, 1H), 5.38 (ddd, 1.4 Hz, 10.6 Hz, 1H), 5.28 (dd, 2.2 Hz, 8.3 Hz, 1H), 5.09 (t, 9.6 Hz, 1H), 4.23 (dd, 5.5 Hz, 12.4 Hz, 1H), 4.09 (m, 2H), 3.89 (s(br), 1H), 3.82 (ddd, 2.3 Hz, 5.22 Hz, 12.9 Hz, 1H), 2.03 (s, 3H), 2.02 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H); $^{13}C\{^1H\}$-NMR (90 MHz, $CDCl_3$, 25°C): δ=171.1 (s), 171.0 (s), 170.9 (s), 169.6 (s), 157.3 (s), 157.2 (s), 138.1 (d), 138.0 (d), 135.5 (d, 20.8 Hz), 134.6 (d, 20.6 Hz), 133.0 (d, 18.3 Hz), 128.4 (d), 128.3 (s), 128.3 (d), 116.7 (d, 7.8 Hz), 115.8 (d, 8.2 Hz), 98.2 (s), 71.8 (s), 69.7 (s), 68.5 (s), 62.0 (s), 53.7 (s), 23.2 (s), 20.6 (s), 20.6 (s), 20.5 (s); $^{31}P\{^1H\}$-NMR (101 MHz, $CDCl_3$, 25°C): δ=−8.6; IR (cm^{-1}, KBr): ν=3289, 2972, 1749, 1663, 1594, 1580, 1497, 1434, 1368, 1228, 1174, 1046, 913, 830, 747, 699.

2.2. *Ligand synthesis by palladium-catalyzed coupling reaction*

2.2.1. *1-O-[4-diphenylphosphino)phenyl]-β-D-galactopyranoside* **3b**

A mixture of **7** (100 mg, 0.18 mmol), diphenylphosphine (34 mg, 0.18 mmol), KOAc (22 mg, 0.22 mmol) and **8** (1 mg, 0.1 mmol) in acetonitrile (2 ml) was refluxed at 130°C in a pressure tube for 12 h. Afterwards 10 ml ethyl acetate was added, the solution was washed (2× water, 2× saturated brine), and dried over $MgSO_4$. After evaporation of the solvent the residue was purified by column chromatography (silica gel 60) (ethyl acetate/hexane 1/2 v/v) and isolated in 85% yield.

2.2.2. *Bis[4-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)phenyl]-phenylphosphine* **3f**

A mixture of **7** (200 mg, 0.36 mmol), phenylphosphine (20 mg, 0.18 mmol), NEt_3 (45 mg, 0.43 mmol) and **8** (1 mg, 0.1 mmol) in acetonitrile (2 ml) was refluxed at 130°C in a pressure tube for 12 h. Afterwards 10 ml ethyl acetate was added, the solution was washed (2× water, 2× saturated brine), and dried over $MgSO_4$. After evaporation of the solvent the residue was purified by column chromatography (silica gel 60) (ethyl acetate/hexane, 1:1, v/v) and isolated in 48% yield.

^1H-NMR (270 MHz, $CDCl_3$, 25°C): δ=7.26 (m, 9H), 6.96 (d, 8.4 Hz, 4H), 5.45 (m, 4H), 5.10 (m, 4H), 4.16 (m, 6H), 2.16 (s, 6H), 2.04 (s, 6H), 2.00(s(br), 12H); $^{13}C\{^1H\}$-NMR (68 MHz, $CDCl_3$, 25°C): δ=170.2 (s), 170.1 (s), 170.0 (s), 169.3 (s), 157.4 (s), 135.2 (d, 22.3 Hz), 134.4 (d, 10.8 Hz), 133.2 (d, 18.7 Hz) 131.1 (d, 9.8 Hz), 128.5 (d, 9.8 Hz), 128.4 (s), 99.2 (s), 71.0 (s), 70.7 (s), 68.5 (s), 66.8 (s), 61.2 (s), 20.7 (s), 20.6 (s), 20.5 (s); $^{31}P\{^1H\}$-NMR (109 MHz, $CDCl_3$, 25°C): δ=−7.9; IR (cm^{-1}, KBr): ν=3061, 3030, 2919, 2853, 1754, 1594, 1495, 1370, 1229, 1076, 830.

2.3. *Measurement of the Nernst partition coefficient α of* **3a**

A definite amount of **3a** (about 5 mg) was dissolved in 4.5 ml ethanol/water (2:1), 4.5 ml isooctane were added and the mixture intensively stirred under an atmosphere of argon in thermostated water bath for about 1 h. In order to measure the ligand concentration in the organic phase, 20 μl of the aqueous and 75 μl of the organic phase were taken out of the mixture and put into a cuvette. The mass of the liquid was exactly measured and diluted with 2 ml ethanol. The mass of the ethanol is also weighed, so the dilution can exactly be calculated. The UV absorbance at 259 nm of the solutions is measured with a Perkin Elmer UV–Vis spectrometer. At every temperature (5.0°C, 25.7°C, 31.5°C and 51.2°C) the concentration of each phase is measured three times and the results averaged (18 measurements at each temperature). Using a calibration curve the concentrations can be calculated from the absorbances. The Nernst partition coefficient at the different temperatures can be calculated from the concentrations of the ligand **3a** in each phase knowing the dilution. For the measuring of the calibration curve

and the Nernst partition coefficient UV grade solvents have to be used. The calibration curve is obtained the following way. A stock solution of **3a** in ethanol is prepared, small definite volumina of this solution are taken out, weighed, diluted with ethanol (2 ml) that is also weighed, and the absorption at 259 nm measured.

2.4. General procedure for the catalytic Suzuki coupling reactions

15 mmol (1.1 equiv) phenylboronic acid **9**, 13.5 mmol aryl bromide **10**, **11a**, or **11b**, and 40.5 mmol (2.7 equiv) $Na_2CO_3 \cdot 10H_2O$ were dissolved in the biphasic mixture (36 ml ethanol/water/toluene (2:1:3) or 36 ml ethanol/water/di-*n*-butylether (2:1:3)). The reaction mixture was pre-heated to 60°C, the catalyst ($Pd(OAc)_2$ and ligand in ethanol/water (1:1) dissolved) added. Then the mixture was refluxed at 78°C for 2 h. Afterwards the organic layer was washed with water and brine, the solvent was evaporated, and the product was isolated by crystallization (**13a** and **13b**) or column chromatography (**12**). All products were characterized by NMR-spectroscopy and were consistent with the literature data.

2.5. General procedure for the catalytic Heck reaction

15 mmol aryl bromide (**14a–b**, **15**), 22.5 mmol olefin (1.5 equiv), 16.5 mmol $NaOAc \cdot 3H_2O$ (1.1 equiv) were suspended in 10 ml xylene and 10 ml ethylene glycol. Ligand and $Pd(OAc)_2$ (Pd/L=1:3) were added in solid form, and the mixture was heated to 130°C for 20 h. After cooling to room temperature methylene chloride and hydrochloric acid (2 N) were added to dissolve the formed products and salts. The organic phase was separated, washed with water and brine and dried over $MgSO_4$. After the solvent was evaporated the products were purified by crystallization from methanol/acetone mixtures or by column chromatography over silica gel 60 with ethyl acetate/hexane and then characterized by NMR and mass spectroscopy.

2.6. General procedure for the catalytic hydroformylations

Two-phase hydroformylation reactions of 1-octene were carried out in a 300 ml stainless steel Parr autoclave with a glass inlet. The pre-catalysts were prepared in situ by mixing $Rh(OAc)_3$ and the required amount of ligand in 30 ml water under an atmosphere of argon and then pressurizing the reaction vessel with 25 bar of syngas and heating up to 125°C for 3 h. After the preformation of the catalyst 30 ml toluene, the substrate (1-octene) and hexadecane (1 ml) as an internal standard for gas chromatographic analysis were added to the pre-catalyst containing solution by a pressure syringe. The reaction mixture was constantly stirred at 1000 min^{-1} for the whole reaction time. After cooling the vessel was depressurized and the organic phase was analyzed by gas chromatography.

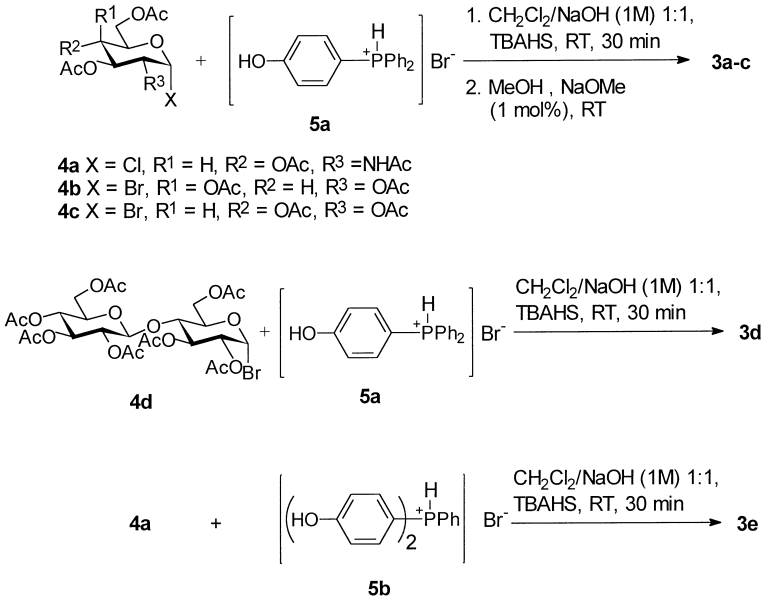
3. Results

3.1. Synthesis of carbohydrate-substituted triarylphosphines

The synthesis of carbohydrate-substituted triarylphosphines has received only very little attention until now. In fact, there is only one report [20] on the glycosidation of hydroxytriarylphosphines with 1-bromo-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside prior to our recent work [15]. However, the reported glycosidation reaction (acetone, KOH, RT, 8 h) proceeds only in 14% yield. Hence, we set out to develop more efficient synthetic procedures.

Our initial experiments to synthesize **3a–c** using α-halopyranoses as glycosyl donor using standard glycosidation procedures[1] also demonstrate the difficulty to combine classical carbohydrate and phosphine chemistry. We attribute the failure of well-known Lewis acid catalysts or heavy metal activators in these glycosidations to a preferential binding of the metal atom to the phosphine. Even with overstoichiometric amounts of Lewis acids no desired reaction takes place probably because of a repulsion of the resulting phosphonium salt and the stabilized sugar cation. Consequently, a different strategy had to be developed which relies on the activation of the glycosyl acceptor instead of the glycosyl donor. Indeed, a biphasic

[1] Koenigs–Knorr conditions, Lewis acid catalysis using BF_3 or TMS–Tf and sugar trichloracetimidate; melting of the sodium ion of **5a** and **4b** under $ZnCl_2$ catalysis.



Scheme 1. Synthesis of ligands **3a–e**.

glycosidation reactions using phase transfer catalysis [21,22] which is believed to proceed through more reactive phenolate anions was successful (Scheme 1).

Thus, the reaction of (*p*-hydroxyphenyl)diphenylphosphoniumbromide (**5a**) and acetyl-protected α-halopyranoses **4a–c** was combined in a biphasic mixture of methylene chloride and sodium hydroxide. Double deprotonation of **5a** takes place under glycosidation conditions, the isolation of (*p*-hydroxyphenyl)diphenylphosphine is not necessary. To optimize this glycosidation method the reaction of **4a** with **5a** in the presence of various phase transfer agents were examined, and the results are summarized in Table 1. Subsequent Zemplén saponification led to the product **3a**.

Best yields of **3a** (68% based on **5a**) are obtained using a five-fold excess of **4a** with tetra-*n*-butylammoniumhydrogensulfate (TBAHS) as phase transfer agent (entry 9). When **5a** was used in excess under otherwise similar conditions, a lower yield of **3a** was produced (52% based on **4a**). Nevertheless, this latter procedure has the advantage that the fully acetylated glycoside can be obtained very easily in pure form by direct crystallization from the reaction mixture. Thus, largescale synthesis (>10 g) of **3a** without chromatographic purification was performed, which is unusual in carbohydrate chemistry. As demonstrated in Table 2 similar glycosidations were realized with **4b** and **4c** as glycosyl donors.

Comparing the different glycosyl donors, the reaction yielding the glucose derivative **3c** proceeded in 33% yield, whereas **3a** and **3b** were obtained with 68% and 50% yield, respectively. As byproducts 2-acetoxyglucals and dihydrooxazoles are observed in case of **3b–c** and **3a**, respectively. The lower yield using **3c** is likely due to steric and electronic factors.

Importantly, all glycosidations proceed with high stereoselectivity. The β-anomer was formed selectively in each case due to the neighboring group effect of the acetyl group at C–2.

Next, we were interested in the synthesis of disaccharide-substituted phosphines and multiple-glycosylated phosphines. Thus, we examined the glycosidation of bis(*p*-hydroxyphenyl)phenylphosphine and tris(*p*-hydroxyphenyl)phosphine with **4a** as glycosyl donor. Unfortunately, **3d** and **3e** were obtained only in 19% and 26% yield, respectively. In case of tris(*p*-hydroxyphenyl)phosphine no desired product could be isolated. As a matter of fact in the multiple-glycosidation reactions, there is always a considerable amount of unglycosidated phosphine left, even if a 10-fold excess of **4a** is used. Therefore,

Table 1
Optimization of reaction conditions for **3a**

Entry	PTC[a]	Yield (%) based on **5a**	Yield (%) based on **4a**	*c*(NaOH) (mol/l)
1	BTEAC[b]	14	27	1
2	TBAB[c]	27	50	1
3	TBAB[c]	24	45	1
4	TBAB[c]	22	45	2
5	TBAF[d]	22	45	1
6	TBATF[e]	10	19	1
7	TBAHS[f]	27	52	1
8	TBAHS[f]	26	49	1
9	TBAHS[f]	68	14	1
10	TBAHS[f]	19	37	2
11	TOAB[g]	20	40	1
12	PEG 400[h]	7	12	1

[a]Phase transfer catalyst.
[b]Benzyltriethylammoniumchloride.
[c]Tetrabutylammoniumbromide.
[d]Tetrabutylammoniumfluoride.
[e]Tetrabutylammoniumtetrafluoroborate.
[f]Tetrabutylammoniumhydrogensulfate.
[g]Tetraoctylammoniumbromide.
[h]Polyethyleneglycol 400.

Table 2
Carbohydrate substituted triphenylphosphines **3a–e**

Compound	Sugar	Yield (%)
3a	Glucosamine	68
3a	Glucosamine	52[a]
3b	Galactose	50[a]
3c	Glucose	33
3d	Cellobiose	19
3e	Glucosamine	26

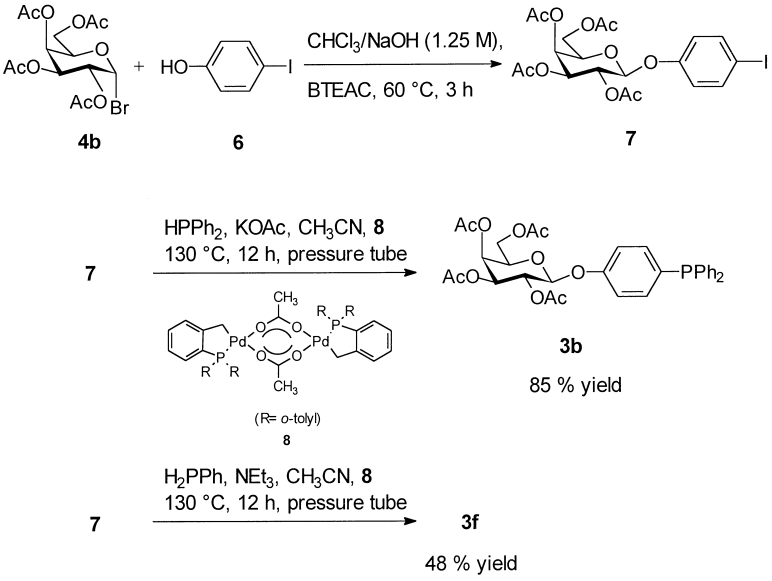
[a]Yield based on **4a** and **4b**, respectively.

we sought alternative pathways to synthesize carbohydrate-substituted triarylphosphines. Based on the elegant palladium-catalyzed coupling reaction of aryl iodides with diphenyl- or phenylphosphine developed by Stelzer et al. [23] we synthesized **3b** and **3f** as depicted in Scheme 2.

1-*O*-(4-Iodophenyl)-2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside **7** was obtained directly from the reaction of **4b** with 4-iodophenol **6** in 70% yield [24]. Again, the reaction was performed in a biphasic mixture consisting of chloroform and aqueous sodium hydroxide using benzyltriethylammonium chloride (BTEAC) as phase transfer catalyst. Subsequently, the palladium-catalyzed coupling of **7** with diphenylphosphine was carried out in acetonitrile as solvent at 130°C in a pressure tube. In our initial attempt, palladium acetate was employed as catalyst for the coupling. In the presence of 0.1 mol% a mixture of various phosphine products was observed. However, using 0.1 mol% of the cyclometallated palladium complex **8** (palladacycle) which was introduced by Herrmann and ourselves as a highly efficient catalyst for C–C coupling reactions [25–28], the reaction proceeded smoothly to one single product (peracetylated **3b**) in 85% yield. Interestingly, this reaction is especially useful for the synthesis of multiple glycosidated triphenylphosphines. Thus, the reaction of phenylphosphine with two equivalents of **7** and NEt_3 as a base yielded **3f** in 48% yield. Therefore, this new synthetic access to carbohydrate-containing phosphines complements the direct glycosidation of hydroxytriarylphosphines and makes multiple glycosidated triphenylphosphines accessible for the first time.

3.2. Properties of the ligands

The new class of carbohydrate-substituted phosphines **3** contains a polar (sugar) and a non-polar



Scheme 2. Synthesis of **3b** and **3f** by palladium-catalyzed P–C coupling reaction.

(triphenylphosphine) moiety. Measurement of the surface tension depression in a toluene/water system provided insight into potential detergent properties of **3a–c** and demonstrated that these are no surfactants and do not form micelles in water. In order to test the ligands for biphasic catalysis it is important to investigate solubility properties and partition coefficients between organic and hydrophilic phases. As one might expect the solubility of **3a–c** in water is low compared to ionic phosphines, but very good in water/alcohol mixtures. This result is not necessarily a disadvantage for biphasic catalysis since the work of Fell et al. [29] demonstrated that the addition of methanol as a co-solvent to water is a general way to improve catalyst activities for two-phase hydroformylation.

As a consequence of the solubility properties of the ligands **3a–c** we determined the Nernst partition coefficient α of **3a** at different temperatures using a biphasic mixture consisting of water, ethanol, and di-*n*-butylether (1:2:3, v/v/v).

As shown in Table 3 there is a partition of the ligand **3a** between the two phases at any temperature investigated. Interestingly, an increase of the value of α of **3a** is observed with higher temperature, indicating a thermoreversible solvation. This phenomenon is also known for phosphines containing polyglycol ethers and is explained by a reversible loss of weakly bound water molecules [30,31]. In principle, the thermoreversible solvation is very attractive for two-phase catalysis due to the higher concentration of the catalyst in the organic phase under the conditions where the catalysis takes place. However, a prerequisite for practical use of this effect is a more distinct change of the α value in between a relatively narrow temperature range. A thermoreversible solvatation is not seen for TPPTS.

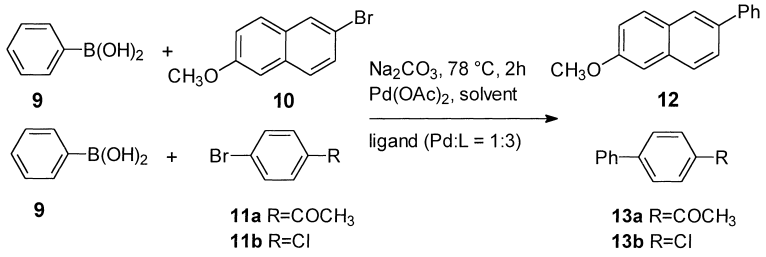
Table 3
Nernst partition coefficient α for **3a** at different temperatures

Temperature (°C)	α^{ab}
5	0.077
25	0.086
30	0.094
50	0.117

[a]Loading (mg **3a**/mg solvent) of the non-polar phase/loading of the polar phase.
[b]Standard deviation 0.001.

3.3. Catalysis of Suzuki reactions

The palladium-catalyzed arylation of aryl halides with aryl boronic acids – generally referred to as the Suzuki coupling [32–35] – has received broad atten-



Scheme 3. Two-phase Suzuki-coupling with TPPTS, **3a** and **3b**.

tion in the last decade. This is primarily due to the increasing importance of unsymmetrically substituted biaryl derivatives, e.g. as drug intermediates. However, a relatively large amount of catalyst (1–5 mol%) is usually needed for reasonable conversions and catalyst recycling is hampered by precipitation of palladium black. These couplings are often performed in biphasic media, however very few examples of Suzuki reactions are known using catalyst systems which are soluble in hydrophilic phases [36–38].

Initial experiments [15] show that carbohydrate-substituted phosphines **3a–b** are suitable ligands to form palladium(0) complexes which catalyze Suzuki couplings of various bromoarenes (**10**, **11a–b**) with phenyl boronic acid (**9**) efficiently (Scheme 3).

As depicted in Scheme 3, the reaction of phenyl boronic acid (**9**) with 2-bromo-6-methoxynaphthalene (**10**), 4-bromoacetophenone (**11a**), and 4-chlorobromobenzene (**11b**) yield the corresponding biphenyls **12**, **13a**, and **13b**, respectively. In general, yields >50% are obtained, while catalyst productivities (TON) range between 550 and 9000. The reaction was complete within 15 min when activated arylbromides were used, as measured by GC. However, reactions were terminated after 2 h for comparison purposes (see Table 4).

Comparing productivity of catalytic systems with the sulfonated ligand TPPTS to catalysts with **3a–b** leads to the conclusion that carbohydrate-substituted phosphines give superior or at least equally performing catalysts.

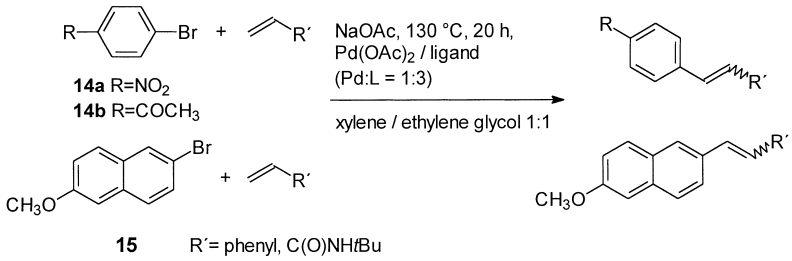
3.4. Catalysis of Heck reactions

In addition to aryl boronic acids, aryl halides can be coupled in the presence of a palladium catalyst, with

Table 4
Palladium-catalyzed Suzuki reaction with TPPTS, **3a** and **3b** as ligands

Entry	Educt	Ligand	Product	Yield (%)[a]	Cal. (mol%)	TON[b]	Solvent
1	**10**	**3a**	**12**	38	0.01	3800	e/w/t[c]
2	**10**	TPPTS	**12**	55	0.1	550	e/w/t[c]
3	**11a**	**3a**	**13a**	87	0.01	8700	e/w/dbe[d]
4	**11a**	TPPTS	**13a**	67	0.01	6700	e/w/dbe[d]
5	**11a**	**3b**	**13a**	90	0.01	9000	e/w/t[c]
6	**11a**	TPPTS	**13a**	87	0.01	8700	e/w/t[c]
7	**11b**	**3a**	**13b**	56	0.01	5600	e/w/dbe[d]
8	**11b**	TPPTS	**13b**	40	0.01	4000	e/w/dbe[d]
9	**11b**	**3b**	**13b**	71	0.01	7100	e/w/t[c]
10	**11b**	TPPTS	**13b**	44	0.01	4400	e/w/t[c]
11	**11b**	**3b**	**13b**	89	0.1	890	e/w/t[c]
12	**11b**	TPPTS	**13b**	92	0.1	920	e/w/t[c]

[a]Isolated yield.
[b]TON=turn over number: mol (product)/mol (catalyst).
[c]Ethanol/water/toluene.
[d]Ethanol/water/di-*n*-butylether.



Scheme 4. Two-phase Heck reaction with TPPTS, **3a** and **3b**.

olefins yielding aryl olefins (Heck reaction) [39–45]. This method is arguably one of the most powerful tools of organic synthesis for generating carbon–carbon bonds. Recently, we developed cyclometallated palladium complexes as highly efficient catalysts or pre-catalysts for the Heck reaction, which also fulfil technical requirements [25–28]. However, catalyst improvements are still desirable. As a continuation of our efforts in this area, we tested ligands **3a–b** for selected palladium-catalyzed Heck olefinations and compared them with TPPTS (see Scheme 4).

The two-phase Heck reaction was carried out with different bromoarenes (**14a**, **b–15**) and styrene as well as *tert.*-butyl acrylic acid amide as terminal olefins. A 1:1 mixture of xylene and ethylene glycol was utilized as biphasic medium. The resulting aryl olefins were isolated either by crystallization or by column chromatography. The formation of stilbenes derived from activated aryl bromides (**14a** and **14b**) and styrene proceeds in the presence of **3a–b** with better results than with TPPTS. Using an acrylic acid amide similar results were obtained for all investigated ligands. We attribute this result to the higher solubility of the polar olefin in the hydrophilic phase. In the case of deactivated aryl bromides, TPPTS proved to generate a more stable, and thus more productive catalyst system compared to **3a–b** (see Table 5).

3.5. Two-phase hydroformylation of 1-octene

Biphasic hydroformylation constitutes one of the major industrial applications of two-phase catalysis [6]. Approximately 3.5 million tons of *n*-butanal have been produced from propene using a rhodium based TPPTS catalyst since the start up of an industrial plant at Ruhrchemie (Hoechst AG) in 1984. Although this elegant process was an enormous breakthrough in hydroformylation technology, so far only propene and to a much lesser extent 1-butene are used as starting materials for biphasic hydroformylation. Although the hydroformylation of higher olefins

Table 5
Heck reaction with TPPTS, **3a** and **3b** as ligands

Entry	ArBr	R	Ligand	Cat. (mol%)	Yield (%)[a]	TON[b]
1	**14a**	Ph	TPPTS	1	73	73
2	**14a**	Ph	**3a**	0.1	81	810
3	**14a**	Ph	**3b**	0.1	88	880
4	**14b**	Ph	TPPTS	1	71	71
5	**14b**	Ph	**3a**	1	87	87
6	**14b**	Ph	**3b**	1	80	80
7	**14b**	C(O)NH^{t}Bu	TPPTS	1	96	96
8	**14b**	C(O)NH^{t}Bu	**3a**	0.1	87	870
9	**15**	Ph	TPPTS	1	66	66
10	**15**	Ph	**3a**	1	52	52

[a]Isolated yield.
[b]TON=turn over number: mol (product)/mol (catalyst).

($>C_8$) with an annual output of >1.5 million tons of oxo products is interesting from an economic point of view, difficulties arise with increasing chain length of the olefin. Due to the low solubility of the olefin in the aqueous catalyst phase, the catalyst productivity is too low for application. According to Fell and co-workers, [30,31] rhodium catalysts based on polyether containing phosphines show improved catalyst activity compared to rhodium TPPTS systems. Hence, we were interested in the performance of carbohydrate-substituted phosphines for the hydroformylation of higher olefins. As a model reaction we studied the hydroformylation of 1-octene under standard oxo reaction conditions (25 bar; 125°C) in water/toluene as solvents. As pre-catalysts in situ mixtures of $Rh(OAc)_3$ with **3a**, TPPTS and TPP as ligands were employed, respectively. These pre-catalysts were activated prior to the reaction by pressurizing the autoclave with 25 bar of synthesis gas (CO/H_2 1:1) and heating it up to 125°C for several hours. Afterwards, a solution of the olefin was added under pressure. In general, a large excess of ligand compared to rhodium (>10:1) was employed. The results of the reaction runs are summarized in Table 6.

As expected, the sulfonated ligand TPPTS exhibited low conversion (7%) under these conditions (entry 1). However, in biphasic experiments using **3a** as ligand (entries 2–4) almost complete conversion of the olefin is observed, and the activity of the catalyst system is reasonable (TOF=200–400 h^{-1}). As shown in Table 6, the *n*/*i*-selectivity is moderate using a 10-fold excess of the ligand. A small increase of the regioselectivity is observed at higher P/Rh-ratio. The superiority of **3a** compared to TPPTS is most likely explained by the higher solubility of the corresponding catalyst in the organic phase. Therefore, we determined the amount of rhodium in the organic phase after the reaction was performed (entries 2 and 3) by atomic absorption spectroscopy. It was found that there is a significant leaching of 55 ppm rhodium for entry 2, and 32 ppm for entry 3.

In order to study how the catalyst derived from **3a** behaves in a homogeneous organic phase three runs (entries 5–7) were carried out in neat toluene. Interestingly, the rhodium triphenylphosphine (TPP) system works about one magnitude better than the catalyst system with **3a** as a ligand (TOF=38 000 versus 4200 h^{-1}). If only the leaching of rhodium to the organic phase in the biphasic experiments is responsible for 1-octene conversion the results in entries 4 and 5 should be better. The homogeneous system with **3a** is only 1 order of magnitude more active (4200 versus 550–230 TOF), although the catalyst amount employed is 2 orders of magnitudes higher.

In conclusion we obtained moderate catalyst activities for the hydroformylation of 1-octene. The *n*/*i*-selectivities are similar to Rh TPP catalysts. Further increase of the hydrophilicity is necessary to reduce the leaching of rhodium to the organic phase.

It is clear from the presented results that a quantitative recovery of the catalytic system is not possible due to the partition of the ligand at any temperature. In order to achieve full recovery the ligands have to show a temperature dependent partition in an even more pronounced way.

Table 6
Hydroformylation of 1-octene[a]

Entry	Condition	Ligand	Cat. (mol%)	Ratio ligand/Rh	Time (min)	Conversion (%)	TOF[b]	*n*/iso ratio
1	Two-phase[c]	TPPTS	0.1	10:1	120	7	35	75:25
2	Two-phase[c]	**3a**	0.1	10:1	120	95	480	71:29
3	Two-phase[c]	**3a**	0.1	20:1	150	94	400	75:25
4	Two-phase[c]	**3a**	0.02	10:1	120	90	230	71:29
5	Homogeneous[d]	**3a**	0.1	20:1	100	95	550	77:23
6	Homogeneous[d]	**3a**	0.001	100:1	180	16	4200	82:18
7	Homogeneous[d]	TPP	0.001	100:1	180	91	38 000	69:31

[a]Reaction conditions: temperature: 125°C, initial pressure: 25 bar, catalyst: $Rh(OAc)_3$/ligand.
[b]TOF: turn over frequency.
[c]30 ml water, 30 ml toluene.
[d]60 ml toluene.

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