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Synthesis of ferrocenylglucose phosphonite and bisphosphinite: Pd(II) and Pt(II) complexes, Pd-catalyzed allylic alkylation

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Abstract—The synthesis and characterization of the new phosphorus containing ligands and the corresponding Pd(II) and Pt(II) complexes are reported. The molecular structure of 4,6-bis-*O*-(diphenylphosphino)-2,3-(ferrocene-1,1′-dicarbonyl)-*O*-methyl-α-D-glucopyranoside was determined by X-ray diffraction methods. The new ligands show good activity (90%) and moderate stereoselectivity (39% ee) in the Pd-catalyzed enantioselective allylic alkylation.

1. Introduction

The synthesis of enantiomerically pure compounds is one of the most important focuses in modern organic chemistry.[1]

Due to pharmacological as well as economic and ecological reasons the use of enantiomerically pure drugs and agro chemicals instead of their racemates should be pursued. In many cases only one of the two enantiomers has the desired activity and the other has no activity or shows undesired side effects.[2,3]

The potential of enantioselective catalysis to provide straightforward and clean processes for the synthesis of enantiomerically pure compounds is very high and this methodology is very important for industrial processes.[4]

Chiral ferrocene derivatives play an important role in catalytic asymmetric syntheses. In particular, in the Pd-catalyzed carbon–carbon and carbon–heteroatom bond formation ferrocene derivatives are efficient ligands.[5,6]

There is a great interest in chiral ligands containing phosphorus as donor atom due to the excellent results in asymmetric synthesis (Fig. 1).[7,8]

Several P-containing sugars or sugar-analogues as efficient enantioselective catalysts are well documented.[9] The availability of carbohydrates, also in enantiomerically pure form, due to their occurrence in nature makes it obvious to use sugars to induce chirality into ligands.

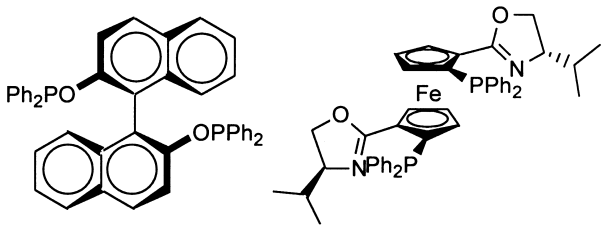

Figure 1. Two P-containing ligands for the allylic substitution:BINAPO (ee 79%) and 1,1′-bis(diphenylphosphino)-2,2′-bis[(*S*)-4-*iso*-propyl-4,5-dihydro-oxazoline-2-yl]-ferrocene (ee 96%).

With this intention we modified ferrocenyl-substituted *O*-methyl-α-D-glucopyranoside with phosphorus-donor components to P-containing glucose-ferrocene derivatives. In addition, we investigated the coordination properties of the synthesized ligands and tested their activity in the Pd-catalyzed allylic alkylation.

2. Results and discussion

The bisphosphinite **2** was synthesized by phosphorylation of 2,3-(ferrocene-1,1′-dicarbonyl)-*O*-methyl-α-D-gluco-pyranoside **1** with Ph_2PCl in 76% yield while the phosphonite **3** was obtained by a similar method from **1** and $PhPCl_2$ in 73% yield (Scheme 1). The characterization of the unstable compound **3** was done as phosphonothioate. This procedure yielded 86% of the (*R*)-product and 14% of the (*S*)-product (72% ee, compare ^{31}P NMR data of **3**). In the literature for

Keywords: phosphonite; phosphinite; ferrocene; catalysis; enantioselective; coordination compound; palladium; platinum.

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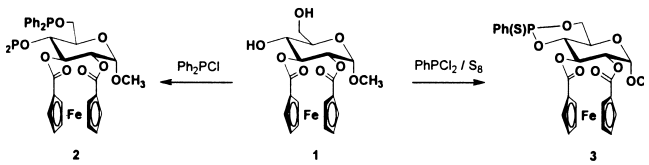


Scheme 1. Reaction scheme for the syntheses of ligands **2** and **3**.

this standard procedure a value of only 16% ee is reported.[10,11]

The ^{1}H, ^{13}C and ^{31}P NMR spectra, the ESI mass spectra and the elemental analyses are in accordance with the structures proposed for the prepared compounds.

It should be noticed that P-couplings to C4 (J_{P-C4}=8.7 Hz) and to C6 (J_{P-C6}=10.7 Hz) in the ^{13}C NMR-spectrum of **3** are recognizable. For compound **2** we found the same effect (J_{P-C4}=5.8 Hz, J_{P-C6}=19.4 Hz). The positive ion ESI mass spectrum of compound **2** shows an intense peak at *m/z* 800 which was assigned to $[M+H]^+$. The fragmentation results in the formation of the $[M-Ph_2POCH_2]^+$ ion with *m/z* 599. For compound **3** a strong peak at *m/z* 593 attributed to $[M+Na]^+$ was observed.

The molecular structure of 4,6-bis-*O*-(diphenylphosphino)-2,3-(ferrocene-1,1′-dicarbonyl)-*O*-methyl-α-D-glucopyranoside **2** was determined by single crystal X-ray diffraction analysis. The result is shown in Fig. 2. The metric parameters of 2,3-{(*R*,*S*)-(ferrocene-1,1′-dicarbonyl)}-*O*-methyl-α-D-gluco-pyranoside skeleton in **2** are very close to those in **1** [CCDC 168911]. The cyclopentadienyl (Cp) rings adopt an arrangement approaching the staggered conformation. The Cp···Fe···Cp torsional twist angle is at 34.7° compared to 29.3° in **1**. Like in **1**, the α-D-glucopyranoside ring adopts a chair conformation. The C(7), C(11), O(3) and C(9) atoms are coplanar within ±0.044 Å. The atoms C(8) and C(10) are on opposite sides of this plane at 0.736 and −0.692 Å. The P(1)···P(2) separation is at 5.201 Å.

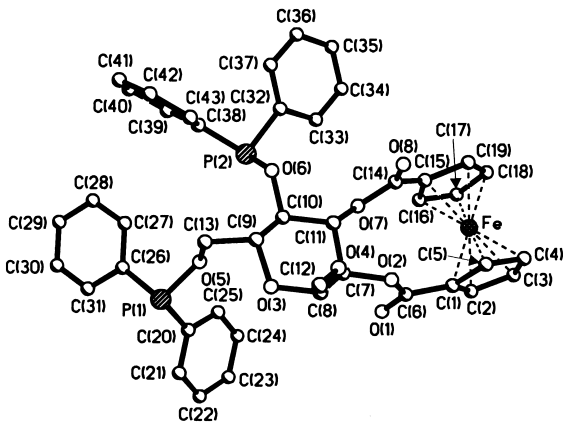
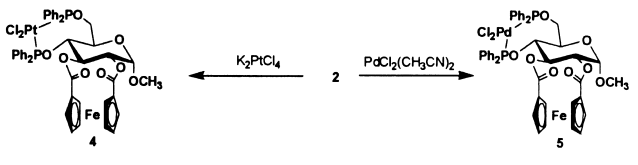


Figure 2. The perspective view of **2**. The H atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): C(7)–C(8) 1.523(2), C(7)–C(11) 1.521(2), C(11)–C(10) 1.515(2), C(10)–C(9) 1.541(2), C(9)–O(3) 1.440(2), O(3)–C(8) 1.422(2), P(1)–O(5) 1.6434(13), P(2)–O(6) 1.6617(12) Å; C(8)–C(7)–C(11) 107.79(13), C(7)–C(11)–C(10) 107.48(13), C(11)–C(10)–C(9) 108.57(13), C(10)–C(9)–O(3) 111.68(13), C(9)–O(3)–C(8) 114.74(12), O(3)–C(8)–C(7) 106.59(13)°.



Scheme 2. Reaction scheme for the syntheses of complexes **4** and **5**.

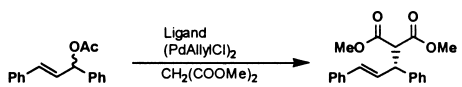
The Pd(II) and Pt(II) complexes of **2** were obtained from $PdCl_2(CH_3CN)_2$ in 90% yield and from K_2PtCl_4 in 72% yield after stirring with **2** for 10 h in CH_2Cl_2 followed by the precipitation with *n*-hexane (Scheme 2).

In the ^{31}P NMR spectra of **4** and **5** P–P-couplings ($^{2}J_{P-Pt-P}$=11 Hz, $^{2}J_{P-Pd-P}$=37.56 Hz) could be observed due to the chelate formation in these compounds. Configuration of compound **4** can be deduced from the following couplings: J_{Pt-P}=4033.2 Hz and J_{Pt-P}=4134.7 Hz. By comparing these data with those documented in the literature[13] we conclude that the Pt(II) complex has *cis*-configuration. The influence of the metal atoms to the spin system of **2** becomes noticeable in the ^{13}C NMR spectrum: a high field shift of the quarternary phenyl carbons for both complexes was observed. The most intense peak in the positive ion ESI mass spectrum of **5** at *m/z* 941 is due to $[M-Cl]^+$ while the peak at *m/z* 999 is related to the $[M+Na]^+$ ion.

The catalytic activities of the ligands **2** and **3** were investigated in the palladium catalyzed allylic alkylation. Asymmetric allylic substitution was carried out with palladium complexes generated in situ by stirring the corresponding chiral ligand and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ under standard conditions (Scheme 3).[12]

Using this procedure we ended up with an enantiomeric excess of 39% for ligand **2** and 28% for ligand **3** (Table 1).

However, a number of catalysis experiments under different conditions were carried out. Using NaH as base instead of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) a dramatic increase in the speed of the reaction could be observed.



Scheme 3. Reaction scheme for the allylic alkylation.

Table 1. Summarized data of the catalytic testing

Ligand[a]	Base	Solvent	Temperature	Time	Yield[b] (%)	ee[c,d] (%)
2	BSA/KOAc[e]	CH_2Cl_2	rt	24	90	39 (*R*)
2	BSA/KOAc[e]	THF	rt	24	85	26 (*R*)
2	BSA/KOAc[e]	CH_2Cl_2	−30°C	36	93	30 (*R*)
2	NaH	CH_2Cl_2	rt	1	98	35 (*R*)
3	BSA/KOAc[e]	CH_2Cl_2	rt	72	70	28 (*R*)

[a] Pd/P=1:2.
[b] Determined by product isolation.
[c] Determined by HPLC (DAICEL CHIRACEL® OD).
[d] Absolute configurations were determined by specific rotation.
[e] BSA/dimethyl malonate/(±)-(*E*)-1,3-diphenylprop-2-en-1-yl acetate=3:3:1, KOAc=cat.

The addition of KOAc might sometimes increase the ee value.[14] However, this is not the case for the ligands **2** and **3**. Possible explanations why the ee is only moderate in comparison to other comparable ligands are:

1. weak influence of the chiral centers to the Pd,
2. flexibility of the 8-membered ring,
3. weak chelate formation or combination of 1–3.

3. Experimental

3.1. General

All reactions were carried out in dry solvents and under argon. The NMR spectra were recorded on a Bruker DPX 400 instrument (Ultrashield™ Magnet) at 400.13 MHz (^{1}H), 100.63 MHz (^{13}C) and 162.00 MHz (^{31}P) at 301 K in $CDCl_3$ with 1% of tetramethylsilane as internal standard. Chemical shifts are reported in δ (ppm) and coupling constants are in Hz. Mass spectra were measured on a Bruker esquire 3000 (ESI). Optical rotations were measured with a Perkin–Elmer 341 polarimeter using a 10 cm cell. Melting points were determined with a Buchi B-540 apparatus and are uncorrected. The elemental analyses were done by the laboratory for elemental analysis of the Institute of Physical Chemistry, University of Vienna, with a Perkin–Elmer 2400 CHN Elemental Analyzer. Silica gel (Fluca 60, 70–230 mesh) was used for column chromatography and silica gel (Polygram® SIL G/UV254) for thin layer chromatography.

3.1.1. 4,6-Bis-*O*-(diphenylphosphino)-2,3-(ferrocene-1,1′-dicarbonyl)-*O*-methyl-α-D-glucopyranoside (2). To a solution of 2,3-(ferrocene-1,1′-dicarbonyl)-*O*-methyl-α-D-glucopyranoside **1** (0.5 g, 1.16 mmol) and NEt_3 (0.24 g, 2.37 mmol) in 10 ml toluene a solution of chlorodiphenylphosphine (0.51 g, 2.32 mmol) in 5 ml toluene was added dropwise for a period of 1 h at 0°C. The reaction mixture was stirred at room temperature for 3 h, filtered and evaporated. The crude product was purified by column chromatography (ethyl acetate/hexane 1:3). Yield: 0.70 g (76%). $[\alpha]_D$=+173 (*c* 0.25, CH_2Cl_2); mp 173–174°C; ^{1}H NMR: δ 7.58–7.30 (m, 17H, Ph-H), 7.15–7.11 (m, 3H, Ph-H), 5.72 (tr, 1H, Glc-H3, ^3J=10.0 Hz), 5.05 (dd, 1H, Glc-H2, ^3J=3.5, 10.0 Hz), 5.01 (m, 1H, Cp-H), 4.93 (m, 1H, Cp-H), 4.81 (d, 1H, Glc-H1, ^3J=3.5 Hz), 4.67 (m, 1H, Cp-H), 4.64 (m, 2H, Cp-H), 4.51 (m, 1H, Cp-H), 4.28 (m, 1H, Cp-H), 4.26 (m, 1H, Cp-H), 4.20 (m, 1H, Cp-H), 4.10–4.03 (m, 3H, Glc-H5,6,6′), 3.53 (s, 3H, OCH_3); ^{13}C{^{1}H} NMR: δ 171.62, 170.51, 142.31, 142.16, 141.99, 141.81, 131.65, 131.41, 131.15, 131.07, 130.93, 130.84, 130.62, 129.84, 129.76, 129.72, 129.53, 128.74, 128.72, 128.64, 128.57, 128.47, 128.39, 98.21, 77.69, 77.19, 76.37, 75.33, 74.96, 73.34, 72.94, 72.68 ($^2J_{C-P}$=5.8 Hz), 72.18, 72.12, 72.01, 71.80, 71.40, 70.90, 69.34 ($^2J_{C-P}$=19.4 Hz), 55.59; ^{31}P{^{1}H} NMR δ 123.8, 118.7. Anal. calcd for $C_{43}H_{38}FeO_8P_2$: C, 64.51; H, 4.78; P, 7.74. Found: C, 64.39; H, 4.75; P, 7.64. MS: 800 *m/z* $[M]^+$.

3.1.2. 4,6-(*R*)- and (*S*)-phenylphosphonothioates-2,3-(ferrocene-1,1′-dicarbonyl)-*O*-methyl-α-D-glucopyranoside (3). To a solution of **1** (0.5 g, 1.16 mmol) and NEt_3 (0.24 g, 2.37 mmol) in 20 ml toluene a solution of dichlorophenylphosphine (0.2 g, 1.16 mmol) in 1 ml toluene was added for a period of 10 min at 0°C. The reaction mixture was stirred at room temperature for 2 h, then sulfur (0.05 g, 1.56 mmol) was added and stirred for another 12 h, filtered and evaporated. The crude product was purified by column chromatography (ethyl acetate/hexane 1:2) to give 0.48 g (73%); mp 159–160°C; ^{1}H NMR: δ 7.75–7.68 (m, 2H, Ph-H), 7.63–7.51 (m, 3H, Ph-H), 5.94 (tr, 1H, Glc-H3, ^3J=10 Hz), 5.15 (m, 1H, Cp-H) 5.14 (dd, 1H, Glc-H2, ^3J=10, 3.5 Hz), 5.05 (m, 1H, Cp-H), 4.85 (d, 1H, Glc-H1, ^3J=3.5 Hz), 4.77 (m, 2H, Cp-H), 4.73 (m, 1H, Cp-H), 4.64 (m, 1H, Cp-H), 4.54 (m, 1H, Glc-H5), 4.43–4.35 (m, 3H, Glc-H4,Cp-H), 4.12–4.04 (m, 2H, Glc-H6,6′), 3.50 (s, 3H, CH_3); ^{13}C{^{1}H} NMR: δ 171.75, 170.69, 132.92, 131.6, 130.46, 130.35, 129.96, 129.82, 99.13, 77.66, 77.59, 76.46, 75.83, 75.45, 73.99, 73.18, 72.61, 72.56, 71.98, 70.90, 70.62, 69.43 ($^2J_{C-P}$=8.7 Hz), 68.94 ($^2J_{C-P}$=10.7 Hz), 63.94 ($^3J_{C-P}$=8.8 Hz), 56.25; ^{31}P{^{1}H} NMR: δ 91.3 (*S*), 80.8 (*R*) (1:7); Anal. calcd for $C_{25}H_{23}FeO_8PS$: C, 52.65; H, 4.07. Found: C, 52.54; H, 4.07. MS: 593 *m/z* $[M+Na]^+$.

3.1.3. Dichloro 4,6-bis-*O*-(diphenylphosphino)-2,3-(ferrocene-1,1′-dicarbonyl)-*O*-methyl-α-D-glucopyranoside platinum(II) (4). A 25 ml flask was charged with **2** (0.1 g, 0.012 mmol), K_2PtCl_4 (0.05 g, 0.012 mmol) and 10 ml of CH_2Cl_2. The orange solution was stirred at room temperature for 10 h, hexane was added and the resulting orange precipitate was filtered and dried in vacuum. Yield 0.092 g (72%). $[\alpha]_D$=+305 (*c* 0.25, CH_2Cl_2); mp 218–219°C (decomp.); ^{1}H NMR: δ 8.10–8.02 (m, 2H, Ph-H), 7.86–7.78 (m, 4H, Ph-H), 7.69–7.25 (m, 11H, Ph-H), 7.16–7.10 (m, 3H, Ph-H), 5.53 (tr, 1H, Glc-H3, ^3J=10 Hz), 5.01 (dd, 1H, Glc-H2, ^3J=3.5, 10.0 Hz), 4.95 (m, 1H, Cp-H), 4.91 (m, 1H, Cp-H), 4.80 (d, 1H, Glc-H1, ^3J=3.5 Hz), 4.67 (m, 1H, Cp-H), 4.62 (m, 2H, Cp-H), 4.44 (m, 1H, Glc-H5), 4.29 (m, 2H, Cp-H), 4.35–4.19 (m, 2H, Glc-H4,6), 3.97 (m, 1H, Cp-H), 3.78 (m, 1H, Glc-H6′), 3.48 (s, 3H, OCH_3); ^{13}C{^{1}H} NMR: δ 171.33, 170.96, 134.26, 134.14, 133.84, 133.71, 133.54, 133.42, 132.69, 132.56, 132.45, 132.22, 130.66, 130.20, 129.86, 129.35, 128.66, 128.53, 128.41, 128.34, 128.23, 98.40, 77.56, 76.96, 76.25, 75.56, 74.99, 73.10, 72.89, 72.59, 72.30, 71.45, 70.78, 70.61, 70.31, 68.73, 68.63, 56.17; ^{31}P{^{1}H} NMR: δ 96.1 ($^2J_{P-P}$=11.0 Hz, J_{P-Pt}=4134.7 Hz), 94.0 ($^2J_{P-P}$=11.0 Hz, J_{P-Pt}=4033.2 Hz). Anal. calcd for $C_{43}H_{38}PtCl_2FeO_8P_2$: C, 48.42; H, 3.59. Found: C, 48.44; H, 3.56.

3.1.4. Dichloro 4,6-bis-*O*-(diphenylphosphino)-2,3-(ferrocene-1,1′-dicarbonyl)-*O*-methyl-α-D-glucopyranoside palladium(II) (5). Following the same procedure as described for **4**, starting from **2** (0.1 g, 0.012 mmol) and $PdCl_2(CH_3CN)_2$ (0.03 g, 0.012 mmol) compound **5** (0.11 g, 90%) was obtained. $[\alpha]_D$=+247 (*c* 0.25, CH_2Cl_2); mp 224–225°C (decomp.); ^{1}H NMR: δ 8.22–8.15 (m, 2H, Ph-H), 7.99–7.86 (m, 4H, Ph-H), 7.70–7.64 (m, 2H, Ph-H), 7.61–7.53 (m, 3H, Ph-H), 7.50–7.44 (m, 2H, Ph-H), 7.43–7.31 (m, 4H, Ph-H), 7.14–7.10 (m, 3H, Ph-H), 5.54 (tr, 1H, Glc-H3, ^3J=10.0 Hz), 5.04 (dd, 1H, Glc-H2, ^3J=3.5, 10.0 Hz), 4.96 (m, 1H, Cp-H), 4.92 (m, 1H, Cp-H), 4.78 (d, 1H, Glc-H1, ^3J=3.5 Hz), 4.67 (m, 1H, Cp-H), 4.63 (m, 1H, Cp-H), 4.62 (m, 1H, Cp-H), 4.30 (m, 2H, Cp-H), 4.27–4.06 (m, 3H, Glc-H4,5,6), 4.00 (m, 1H, Cp-H), 3.78 (m, 1H, Glc-H6′),

3.41 (s, 3H, OCH_3); $^{13}C\{^1H\}$ NMR: δ 171.37, 171.00, 134.28, 134.15, 134.09, 133.95, 133.73, 133.62, 133.23, 133.10, 132.77, 132.60, 132.55, 132.41, 130.92, 130.57, 130.29, 129.87, 128.88, 128.82, 128.78, 128.70, 128.67, 128.55, 128.44, 98.43, 76.92, 75.77, 75.59, 75.04, 73.13, 72.89, 72.61, 72.34, 71.51, 70.77, 70.63, 70.26, 69.33, 69.24, 67.84, 56.16; $^{31}P\{^1H\}$ NMR: δ 125.4 ($^2J_{P-P}$= 37.56 Hz), 123.1 ($^2J_{P-P}$=37.65 Hz). Anal. calcd for $C_{43}H_{38}PdCl_2FeO_8P_2$: C, 52.81; H, 3.92. Found: C, 52.75; H, 3.81. MS: 999 *m/z* $[M+Na]^+$.

X-Ray diffraction data for **2** were collected on a Nonius Kappa CCD diffractometer. The single crystal was positioned at 35 mm from the detector. A total of 360 frames were measured, each for 45 s over 2° scan. $C_{43}H_{38}FeO_8P_2$, formula weight=800.52, monoclinic, space group $P2_1$ (no. 4), a=8.507(2), b=21.315(4), c=11.070(2) Å, β=109.42(3)°, V=1893.1(7) Å^3, Z=2, $d_{calc.}$=1.404 g cm^{-3}, μ=5.38 cm^{-1}, $F(000)$=832, T=120 K; 9246 unique reflections observed, number of parameters: 640. Refinement of the data converged at $R1$=0.0275, $wR2$=0.0625 and Flack parameter at −0.004(7). Full details for the structure reported have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 171374. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk].

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