Low-pressure carbonylation of benzyl bromide with palladium complexes modified with PNS ($PNS = Ph_2PCH_2CH_2C(O)NHC(CH_3)_2CH_2SO_3Li$) or $P(OPh)_3$. Structural identification of palladium-catalyst intermediate

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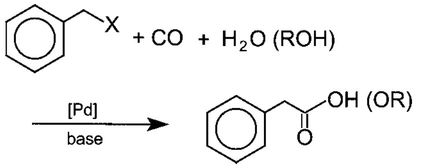
The catalytic activities of two palladium complexes with water soluble phosphine PNS ($PNS = Ph_2PCH_2CH_2C(O)NHC(CH_3)_2CH_2SO_3Li$) (I) and phosphite $P(OPh)_3$ (II) were tested in the carbonylation of benzyl bromide in methanol at 40–50 °C and 1 atm of CO. The first catalyst, (I), was formed *in situ* from $PdCl_2(cod)$ and PNS, the second one, (II), was based on the $PdCl_2(P(OPh)_3)_2$ complex. At the ratio of $[NEt_3]:[PhCH_2Br]$ equal to 2.5 the yields of phenylacetic acid methyl ester were 83–86% in the carbonylation with PNS and 100% in the carbonylation with $P(OPh)_3$. The palladium catalyst with $P(OPh)_3$ produced under the same conditions 70% of phenylacetic acid methyl ester in the carbonylation of benzyl chloride and 60% of 2-methylphenylacetic acid methyl ester in the carbonylation of 1-bromoethylbenzene. The lower rate of carbonylation of 1-bromoethylbenzyl bromide in comparison to that of benzyl bromide was explained by the lower rate of the substrate oxidative addition step leading to palladium benzyl complexes. Two palladium benzyl complexes, *cis*-$PdBr(PhCH_2)(P(OPh)_3)_2$ and *trans*-$PdBr(PhCH(Me))(P(OPh)_3)_2$ have been isolated and characterized (X-ray, ^{31}P and ^1H NMR).

KEY WORDS: carbonylation; benzyl bromide; palladium catalyst; water soluble phosphine

1. Introduction

The carbonylation of aryl and benzyl halides catalysed by palladium complexes is a very promising method of synthesis of carboxylic acids and their derivatives [1–3],



In this paper we demonstrate the high catalytic activity in carbonylation under mild conditions (1 atm CO, 40–50 °C) of two palladium systems modified with different phosphines – the water soluble PNS ($PNS = Ph_2PCH_2CH_2C(O)NHC(CH_3)_2CH_2SO_3Li$) and the hydrophobic $P(OPh)_3$.

The palladium catalyst with the water soluble phosphine PNS was previously tested by us in the carbonylation of benzyl bromide under 10 atm of CO and at 50–130 °C [4]. The results obtained, especially by mechanistic studies, warranted the prediction that it would show a high degree of activity also at milder conditions. The palladium catalyst with $P(OPh)_3$ was successfully applied in the carbonylation of benzyl alcohols in supercritical CO_2 [5]. Our preliminary studies demonstrated its activity also in methanol, at 1 atm of CO [6].

The aim of the studies presented in this paper was to test the catalytic activity of both systems in the carbonylation of different substrates – benzyl bromide and chloride as well as iodobenzyl alcohol.

2. Experimental

$PdCl_2(cod)$ [7], $PdCl_2(P(OPh)_3)_2$ [8], $Pd(P(OPh)_3)_4$ [8], and PNS [9] were obtained according to the literature methods.

The solvents (methanol, toluene) and NEt_3 were purified using standard procedures [10].

2.1. Preparation of cis-$PdBr(CH_2Ph)(P(OPh)_3)_2$ [8]

To a solution of 0.06 g of $Pd[P(OPh)_3]_4$ in benzene (2 cm^3) was added $PhCH_2Br$ (0.1 cm^3) under dinitrogen and the solution was stirred for 30 min. The solution volume was reduced under vacuum to *ca.* 1 cm^3, 1 cm^3 of EtOH was added, and the solution was left for crystallization in a refrigerator. Yield 70%. A crystal suitable for X-ray examination was taken directly from the solution.

^1H NMR ($CDCl_3$, $T = 297$ K) δ 4.50, 4.67 (d, d, 2H, CH_2); ^{31}P NMR ($CDCl_3$, $T = 297$ K) δ 105.0, 113.5 (d, d, ^2J(P–P) 139 Hz); UV-vis ($CHCl_3$) 290, 356; anal. calcd. for $C_{43}H_{37}P_2O_6BrPd$: C 57.51, H 4.15; found: C 57.40, H 4.00.

2.2. Preparation of $PdBr(CH_2Ph)(P(O\text{-}o\text{-}MeC_6H_4)_3)_2$

This complex was obtained as described above with 60% yield.

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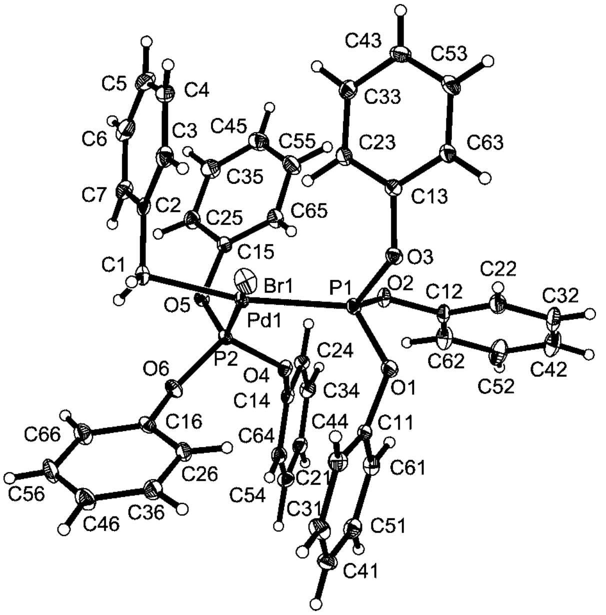


Figure 1. Molecular structure of *cis*-PdBr(CH_2Ph)($P(OPh)_3)_2$.

^{31}P NMR ($CDCl_3$, $T = 297$ K) 103.6 (broad); ($CDCl_3$, $T = 253$ K) δ 104.8, s; 103.85, 109.9 (d, d, ^2J(P–P) 141 Hz); UV-vis ($CHCl_3$) 294, 366; anal. calcd. for $C_{49}H_{49}P_2O_6BrPd$: C 59.92, H 5.03; found C 59.6, H 4.97.

2.3. Carbonylation reaction

The carbonylation reaction was carried out in a 50 cm^3 thermostated glass reactor. Appropriate volumes of the liquids (solvent and triethylamine) were introduced into the reactor in an N_2 atmosphere. The palladium complex and the phosphite were weighed in small Teflon vessels and placed in the reactor. The atmosphere was changed to CO and an appropriate volume of aryl halide was introduced. After the reaction, the reactor was cooled down, and HCl (35%) was added until pH reached *ca.* 7. Organic products were extracted with diethyl ether and analysed by the GC-MS method.

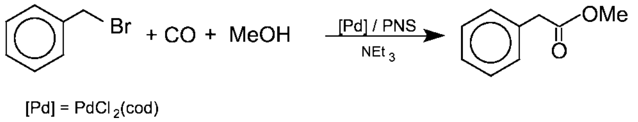
2.4. X-ray

Crystal data are presented in table 5, together with refinement details. All measurements of crystal were performed on a Kuma KM4CCD κ-axis diffractometer with graphite-monochromated Mo Kα radiation. The crystal was positioned at 65 mm from the KM4CCD camera. 612 frames were measured at 0.75° intervals with a counting time of 20 s. The data were corrected for Lorentz and polarization effects. No absorption correction was applied. Data reduction and analysis were carried out with the Kuma Diffraction (Wrocław) programs. The structure was solved by direct methods (program SHELXS97 [11]) and refined by the full-matrix least-squares method on all $F2$ data using the SHELXL97 [12] programs. Non-hydrogen atoms were refined with anisotropic thermal parameters; hydrogen atoms were included from geometry of molecules and $\Delta\rho$ maps and were refined with isotropic thermal parameters.

3. Results and discussion

3.1. Carbonylation of benzyl bromide with catalyst $PdCl_2(cod)/PNS$ (I)

The results of carbonylation of benzyl bromide with a palladium catalyst modified by PNS are presented in table 1.



It can be concluded from these data that two parameters have considerable influence on the yield of phenylacetic acid methyl ester: the concentration of the amine (NEt_3) and the concentration of the phosphine (PNS). At the [NEt_3] : [$PhCH_2Br$] molar ratio equal to 1.7, a yield of *ca.* 30% was achieved in 2 h which did not increase when reaction time was extended. Further experiments were performed with a slightly higher concentration of palladium and benzyl bromide (with the same ratio of [$PhCH_2Br$] : [Pd] as before) at 50 °C. Some increase in the yield was noted, but much better results were obtained when a higher concentration of triethylamine was used. At the ratio of [NEt_3] : [$PhCH_2Br$] equal to 2.5 the yield of the ester already at 40 °C was 61–83%, depending on the excess of PNS. At a two-fold excess of PNS over palladium 61% of the ester was obtained, and the yield increased to 78–83% when the [PNS] : [Pd] ratio was 4 and 6, respectively. These carbonylation yields remained practically unchanged when the temperature was increased to 50 °C.

At the optimal concentrations of the reagents ([NEt_3] : [$PhCH_2Br$] 2.5; [PNS] : [Pd] 4) two experiments were performed in water and water/toluene, giving 76 and 68% of phenylacetic acid, respectively.

Table 1
The yields of phenylacetic acid methyl ester obtained in the carbonylation of benzyl bromide in methanol with the $PdCl_2$(cod)/PNS catalytic system at 1 atm of CO.

[PNS]/[Pd]	Time (h)	Yield of $PhCH_2COOMe$ (%) at reaction conditions			
		[NEt_3]/[$PhCH_2Br$] 1.7		[NEt_3]/[$PhCH_2Br$] 2.5[c]	
		[a]; 40 °C	[b]; 50 °C	40 °C	50 °C
2	2	25	44	61	63
	4	27	47		
	5	27	51		
4	2	20	50	78	78
	4	32	70		
	5	34	70		
6	2	32	32	83	86
	4	32	44		
	5	32	49		

[a] [Pd] 5 × 10^{-3} M, [$PhCH_2Br$] 0.93 M; solvent methanol 1.5 cm^3.
[b] [Pd] 7 × 10^{-3} M, [$PhCH_2Br$] 1.39 M; solvent methanol 1.5 cm^3.
[c] [Pd] 7 × 10^{-3} M, [$PhCH_2Br$] 1.19 M; solvent methanol 1.5 cm^3.

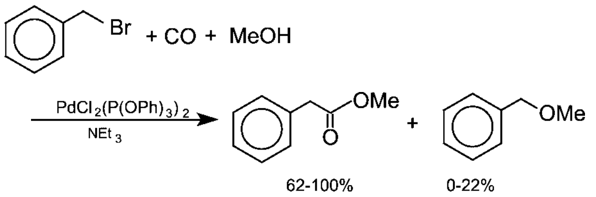
Table 2
The yields of phenylacetic acid methyl ester obtained in the carbonylation of benzyl bromide in methanol with $PdCl_2(P(OPh)_3)_2$ at 40 °C and 1 atm of CO.[a]

Time (min)	$PdCl_2(P(OPh)_3)_2$	$PdCl_2(P(OPh)_3)_2$ + $2P(OPh)_3$	$PdCl_2(P(OPh)_3)_2$ + $4P(OPh)_3$
15	92	75	n.m.[b]
30	98	96	n.m.
60	100	100	62

[a] Reaction conditions: [Pd] 7×10^{-3} M, $[PhCH_2Br]$ 1.19 M, $[NEt_3]$ 3.0 M.
[b] n.m. – not measured.

3.2. Carbonylation of benzyl bromide with catalyst $PdCl_2(P(OPh)_3)_2$ (II)

Under the applied reaction conditions (1 atm CO, 40 °C), with $PdCl_2(P(OPh)_3)_2$ as the catalyst, a yield of 92% of phenylacetic acid methyl ester was obtained after just 15 min, and after 30 min practically total conversion of the substrate to ester was achieved.



During the reaction, however, some amount of metallic palladium was also formed. To prevent palladium reduction, an excess of $P(OPh)_3$ was added to the system. As a result, the carbonylation reaction slightly slowed down, but after 1 h the ester was obtained with a yield of 100% without visible palladium reduction. Experiments performed at different concentrations of $P(OPh)_3$ led to the conclusion that *ca.* 2 mole of $P(OPh)_3$ per mole of $PdCl_2(P(OPh)_3)_2$ is an optimal amount for the highest yield of the ester. When a larger excess of $P(OPh)_3$ was used, selectivity dropped down, and only 62% of the ester was produced together with 22% of benzyl methyl ether. A dramatic lowering of selectivity was noted in a reaction carried out without stirring, which gave only 28% of the ester and almost the same amount of benzyl methyl ether (31%).

Some experiments were performed with the catalyst formed *in situ*, from $PdCl_2(cod)$ and $P(OPh)_3$. Quite satisfactory results were obtained – 84 and 87% of the ester at the $[P(OPh)_3]:[Pd]$ ratio equal to 2 and 4, respectively.

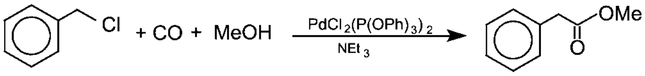
It should be pointed out that during the reaction in methanol, $P(OPh)_3$ can undergo transesterification to $P(OMe)_3$. We did not investigate the extent to which this reaction takes place in the catalytic system, but we isolated palladium complexes (*e.g.*, $[PdBr(CH_2Ph)(P(OPh)_3)]_2$ with $P(OPh)_3$ ligands from the methanol solution containing benzyl bromide and NEt_3 [13]. Similarly, $PdCl_2(P(OPh)_3)_2$ was obtained from $PdCl_2(cod)$ and $P(OPh)_3$ in methanol with a yield of 85%. However, when the solution of $P(OPh)_3$ in methanol was left for 60 min before $PdCl_2(cod)$ addition, $PdCl_2(P(OMe)_3)_2$ was isolated as the main product (60% yield).

Table 3
The yields of phenylacetic acid methyl ester obtained in the carbonylation of benzyl chloride in methanol with $PdCl_2(P(OPh)_3)_2$ at 40 °C and 1 atm of CO.[a]

Time (min)	$PdCl_2(P(OPh)_3)_2$	$PdCl_2(P(OPh)_3)_2$ + $2P(OPh)_3$
15	9	n.m.[b]
30	31	14
60	49	27
120	49	41
180	n.m	43
240	n.m	62
480	n.m	71

[a] Reaction conditions: [Pd] 7×10^{-3} M, $[PhCH_2Cl]$ 1.19 M, $[NEt_3]$ 3.0 M.
[b] n.m. – not measured.

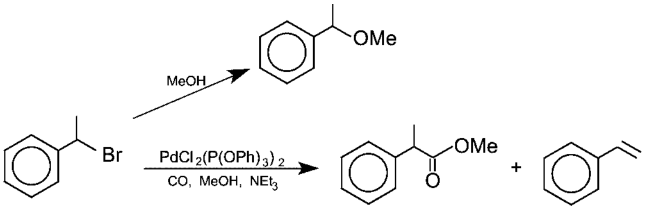
3.3. Carbonylation of benzyl chloride with catalyst $PdCl_2(P(OPh)_3)_2$ (II)



The carbonylation of benzyl chloride proceeded at a lower rate than that of benzyl bromide and stopped at an ester yield of *ca.* 50% when $PdCl_2(P(OPh)_3)_2$ was used as catalyst, probably because of palladium reduction. The addition of excess $P(OPh)_3$ caused a decrease in the reaction rate, but stabilized the active catalyst and after 8 h the yield increased to 71%. The selectivity of ester formation is higher than when benzyl bromide was used as a substrate. This is because the ether is not formed under the reaction conditions applied.

3.4. Carbonylation of 1-bromoethylbenzene (II)

The carbonylation of 1-bromoethylbenzene with $PdCl_2$ $(P(OPh)_3)_2$ as the catalyst is less selective compared with that of benzyl bromide.



Besides the ether, which is formed in the non-catalytic process from the substrate and methanol, some amounts (10–25%) of styrene were found in the reaction products. The formation of styrene can be explained by β-elimination of a proton from the intermediate palladium–benzyl complex, a process that competes with CO insertion into the Pd–C bond.

The carbonylation performed with $PdCl_2(P(OPh)_3)_2$, without free $P(OPh)_3$ added, gave 27% of the ester in 30 min, but because of palladium metal formation the reaction stopped. With the addition of $P(OPh)_3$, the reaction led

Table 4
The products[a] of the carbonylation of 1-bromoethylbenzene in methanol with $PdCl_2(P(OPh)_3)_2$ at 40 °C and 1 atm of CO.

$[P(OPh)_3]/[Pd]$	Time (h)	Ester[b]	Styrene	Ether[c]
0	1	26	10	17
1	1	47	25	8
2	1	47	21	9
2	3	64	21	10
3	3	55	20	16
4.5	3	23	18	10

[a] Besides of products given in the table an unreacted substrate was found in the post-reaction mixture. Reaction conditions: [Pd] 7×10^{-3} M, $[PhCH_2Br]$ 1.2 M, $[NEt_3]$ 3.0 M, methanol 1.5 cm^3.

[b] PhCH(Me)CO(O)Me.

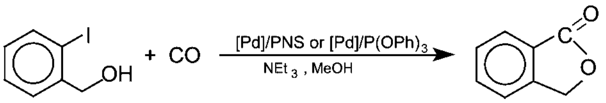
[c] PhCH(Me)OMe.

to a higher yield of the ester, up to 70% at a two-fold excess of $P(OPh)_3$ over $PdCl_2(P(OPh)_3)_2$. At higher concentrations of $P(OPh)_3$ the reaction was slower, and only 23–27% of the ester was formed in 3 h.

For comparison, 2-bromoethylbenzene ($PhCH_2CH_2Br$) was used as a substrate for carbonylation under the same conditions with $PdCl_2(P(OPh)_3)_2$ and a two-fold excess of $P(OPh)_3$. However, only traces (less than 1%) of the ester were found in the reaction products.

3.5. Carbonylation of iodobenzyl alcohol (I) and (II)

The carbonylation of iodobenzyl alcohol in methanol yields selectively only one product, benzylfuranone, formed by intramolecular cyclization,



Both systems produced comparable amounts of carbonylation reaction product, up to 30% at 1 atm of CO and 40 °C. At 5 atm of CO the yield was slightly higher – up to 50%.

Table 5
Selected bond lengths (Å) and angles (°) in *cis*-$PdBr(CH_2Ph)(P(OPh)_3)_2$.

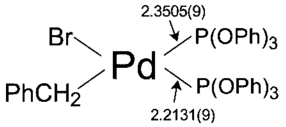
Pd(1)–C(1)	2.135(3)
Pd(1)–P(2)	2.2131(9)
Pd(1)–P(1)	2.3505(9)
Pd(1)–Br(1)	2.4942(8)
C(1)–C(2)	1.498(4)
C(1)–Pd(1)–P(2)	85.93(9)
C(1)–Pd(1)–P(1)	169.41(9)
P(2)–Pd(1)–P(1)	101.10(3)
C(1)–Pd(1)–Br(1)	89.79(9)
P(2)–Pd(1)–Br(1)	164.03(2)
P(1)–Pd(1)–Br(1)	85.48(3)
C(2)–C(1)–Pd(1)	103.01(19)

Table 6
Crystal data and structure refinement.

Empirical formula	$C_{43}H_{37}O_6P_2BrPd$
Formula weight	897.98
Temperature (K)	100(2)
Wavelength (A)	0.71073
Crystal system	Monoclinic
Space group	$P2_1/n$
a (Å)	12.411(2)
b (Å)	22.924(5)
c (Å)	14.193(3)
β (°)	103.67(3)
Volume ($Å^3$)	3923.7(13)
Z	4
D_c ($mg\,m^{-3}$)	1.520
Absorption coefficient (mm^{-1})	1.620
$F(000)$	1816
Crystal size (mm)	$0.20 \times 0.10 \times 0.10$
Diffractometer	Kuma KM4CCD
θ range for data collection (°)	3.38–28.82
Index ranges	$-16 \geqslant h \geqslant 15$, $-31 \geqslant k \geqslant 30$, $-18 \geqslant l \geqslant 15$
Reflections collected	26763
Independent reflections	9412 ($R_{int} = 0.0312$)
Data/parameters	9412/626
Goodness-of-fit (F^2)	1.106
Final R_1/wR_2 indices ($I > 2\sigma I$)	0.0403/0.1074
Largest diff. peak/hole ($e\,Å^{-3}$)	1.041/−1.542

3.6. Structural determination of palladium-catalyst intermediates. X-ray structure of cis-PdBr(CH₂Ph)(P(OPh)₃)₂

According to the well accepted mechanism of carbonylation of aryl halides [14,15], in the first step of this reaction the substrate undergoes oxidative addition to a palladium(0) complex. For model studies we selected the $Pd(P(OPh)_3)_4$ complex, obtained by the reduction of $PdCl_2(P(OPh)_3)_2$ with $NaBH_4$. $Pd(P(OPh)_3)_4$ reacts with benzyl bromide forming a benzyl complex, *cis*-$PdBr(CH_2Ph)(P(OPh)_3)_2$ in a few minutes. ^{31}P NMR spectra of the isolated species as well as spectra measured *in situ* represented two doublets confirming the *cis* position of both the $P(OPh)_3$ ligands. X-ray studies proved the same structure also in solid form. The two Pd–P bonds are non-equivalent with the Pd–P bond *trans* to the benzyl ligand being markedly longer, 2.3505(9) Å, pointing to a strong *trans* influence. The shorter Pd–P bond, *trans* to Br is 2.2131(9) Å,



Similar benzyl complexes with triphenylphosphine $PdX(CH_2Ph)(PPh_3)_2$ (X = Cl, Br, I) were characterized only in solution as *trans* isomers [16,17], which can be explained by the bulkiness of the PPh_3 ligand (Θ 145°) [18] compared with $P(OPh)_3$ (Θ 128°) [18]. In fact, when Pd(P(O-*o*-$MeC_6H_4)_3)_4$ (Θ 141°) reacted with benzyl bromide, a mixture of *cis* and *trans* isomers of $Pd(CH_2Ph)(Br)[P(O\text{-}o\text{-}MeC_6H_4)_3]_2$ was obtained, and the ^{31}P NMR spectrum showed a singlet at 104.8 ppm derived from the *trans* isomer and two double doublets (at 103.9 and 109.9 ppm) with the coupling constant J(P–P) 141 Hz characteristic for the *cis* isomer.

The oxidative addition of 1-bromoethylbenzene to $Pd(P(OPh)_3)_4$ was slower than that of benzyl bromide, and ^{31}P NMR spectra measured *in situ* 30 min after mixing the reagents did not show any new product. However, the complex *trans*-$PdBr(PhCH(Me))(P(OPh)_3)_2$ was identified in solution next day. The structure of the complex was confirmed by the presence of a singlet in ^{31}P NMR (at 94.3 ppm) as well as a multiplet at 4.15 ppm in ^{1}H NMR assigned to a CH proton. The steric hindrance of the Me group of the ethylbenzene ligand (PhCH(Me)) influenced the rate of the oxidative addition of PhCH(Me)Br to the Pd(0) complex as well as the *trans* geometry of the product. Both facts determined the total yield of the carbonylation reaction, which was lower than in the case of benzyl bromide.

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