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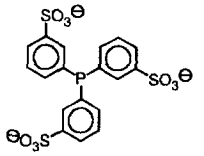
Synthesis and Investigation of Phosphine Ligands Containing Cationic Guanidino Functions in Aqueous Heck Reactions

Harald Dibowski and Franz P. Schmidtchen*

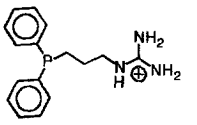
Institut für Org. Chemie und Biochemie, Technische Universität München
D-85747 Garching, Germany; Fax ++49-89-3209-3345

Abstract: Phosphines **2** and **3** supplemented with strongly basic and hydrophilic guanidinium functions were prepared for the first time. In combination with palladium acetate these ligands form active catalysts that promote an aqueous Heck reaction.

Water as a solvent for organic reactions bears a number of attractive features that are increasingly recognized [1,2]. Even organometallic reactions, which at first sight seem to be incompatible with protic solvents, have been successfully conducted in water [3]. Among them palladium catalyzed C-C cross-coupling reactions occupy prominent positions due to the ready availability of quite a number of charged phosphine ligands which render the catalytically active palladium complexes water soluble [4]. Sulfonated triarylphosphines (e.g. triphenylphosphine trissulfonate, tppts **1**) are the most popular ligands and an isolated palladium complex containing the respective monosulfonated triarylphosphine was effective in the cross-coupling of certain nucleotides[5]. One can imagine, however, that the transformation of biologically relevant substrates, which preferentially contain anionic functions (carboxylates, phosphates) would be better served by cationic phosphine ligands since they avoid the putative inhibitory electrostatic repulsion accompanying the use of sulfonated ligands. Cationic phosphines, which are stable under the basic conditions involved in most palladium catalyzed cross-couplings so far exclusively contained quaternary ammonium functions [4]. Though this group is chemically inert and confers limited water solubility we reasoned that the introduction of one of the most basic and hydrophilic functional groups [6], the guanidinium moiety, would be a better choice. In addition, as was evident from the anion binding rôle of the guanidinium side chain of arginine in natural receptors [7] and its wide-spread use in artificial hosts [8,9], one can expect some directing influence on the conversion of oxoanionic substrates. Here we report on the synthesis of the guanidino phosphines **2** and **3** and on preliminary studies to use these ligands in a prototypical Heck reaction in water.



1



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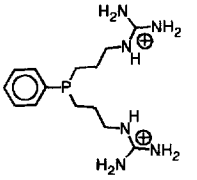
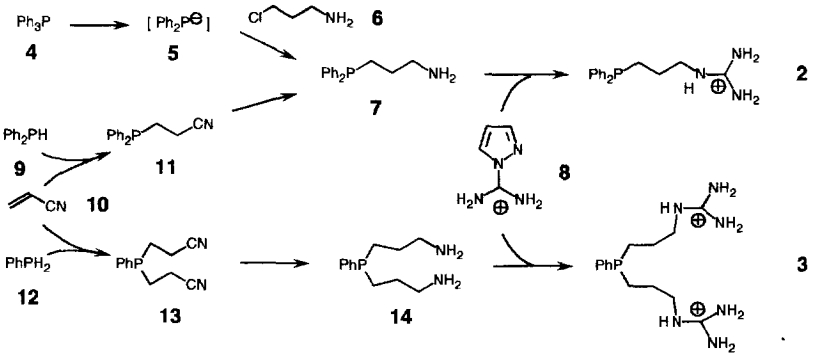


3

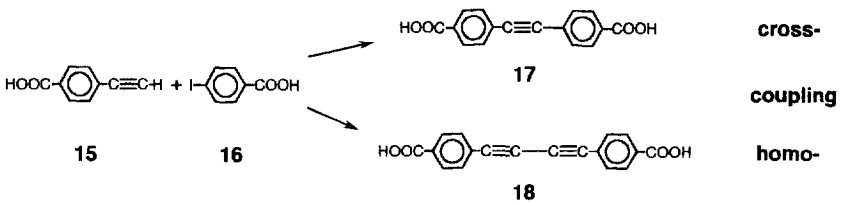
Monoguanidino phosphine **2** is accessible by two routes with comparable success (scheme 1): Diphenylphosphide anion **5** was generated by cleavage of triphenylphosphine **4** with sodium in liquid ammonia and alkylated by 3-chloropropylamine **6** [12] to give amine **7** (67%). Alternatively, commercial diphenyl-

phosphine **9** was added to acrylonitrile in a Michael reaction to yield the nitrile **11**[10](84%). Reduction of the cyano group by $LiAlH_4$ in ether gave the primary amine **7** (69%), which was converted into the corresponding guanidinium salt **2** by 1H-pyrazole-1-carboxamidine **8**[11] under basic conditions in DMF (70%). The preparation of the bisguanidino ligand **3** was achieved by using very similar chemistry as described. Double Michael addition of phenylphosphine **12** to a slight excess of acrylonitrile in acetonitrile yielded the bis adduct **13** (58%) which underwent reduction ($LiAlH_4$, 75%) and finally guanidylation (reagent **8**, 60%) as expected.
Scheme 1



The cationic phosphines **2** and **3** both are readily soluble in water (as acetates or chloride salts), the latter reaching the solubility of tppts **1**. Compared to anionic **1** the guanidino phosphines are considerably less susceptible to oxidation. The palladium complex formed *in situ* with tppts **1** (Pd / ligand = 1:5) was destroyed completely by 1.5% H_2O_2/H_2O at 25°C overnight with precipitation of black palladium oxides. The complexes of **2** and **3** survived the same conditions largely untouched (no precipitate, the HPLC peaks of the complexes were reduced by 30% (**2**) or 10% (**3**), respectively). The greater stability might be a consequence of a diminished overall basicity at the phosphorous and might thus hamper the ligating properties. However, the improved air stability definitely helps in purification and would also add to the durability of a catalytic system.

In order to test these compounds as ligands in a palladium-catalysed C-C coupling we selected the Heck-reaction between 4-iodobenzoic acid **16** and p-carboxyphenylacetylene **15** as a simple model system.
Scheme 2



Under the aqueous basic reaction conditions at 50°C substrates as well as products carry negative charges and form a homogeneous solution. The composition was examined by gradient HPLC (Nucleosil RP-18, 10 to 90% MeOH/ 0.03 M H_3PO_4) and the individual coupling products were identified by comparison with independently synthesized authentic material (quantification by peak height). The catalyst was formed *in situ* by addition of a stock solution of Pd-acetate/ligand in a 1:5 mol ratio.

Table 1: Heck coupling of **15** and **16** in plain water at 50 °C in the presence of 0.05 M K_2CO_3 using 5 mol% Pd; product analysis and kinetics by HPLC; peak height ratios at λ = 254 nm are given; conversion refers to the consumption of alkyne **15**.

additive			10 mol% CuI	
	react. time [h] (conversion)	cross/homo coupling	react. time [h] (conversion)	cross/homo coupling
tppts **1**	20 (100)	1 / 1	<3 (100)	∞
ligand **2**	40 (40)	1 / 1	3 (33)	1 / 1.5
ligand **3**	40 (40)	2 / 1	1 (60)	1 / 1

When conducted in water the reaction was catalyzed by any of the palladium-ligand systems (ligand **1, 2, 3**), although at a rather sluggish pace (Table 1). Addition of copper iodide accelerated the reactions by more than ten times and confirmed that catalysis by tppts **1** was considerably faster than with the cationic ligands **2** and **3**. Moreover, the chemoselectivity of cross-coupling versus homo-coupling (Scheme 2), which was rather similar for all ligands in the absence of copper cocatalyst, improved greatly, but only for the anionic phosphine.

Table 2: Heck coupling of **15** and **16** (0.01 M each) in 50 % acetonitrile/water at 50 °C using 5 mol% Pd and 10 mol% CuI; conditions for analysis as given in Table 1.

base	0.05 M K_2CO_3		0.02 M $N(C_2H_5)_3$		0.05 M $N(C_2H_5)_3$	
	react. time [h] (conversion)	cross/homo coupling	react. time [h] (conversion)	cross/homo coupling	react. time [h] (conversion)	cross/homo coupling
tppts **1**	0.3 (100)	∞	2 (100)	∞	1.5 (100)	9 / 1
ligand **2**	0.3 (30)	2 / 1	0.5 (15)	2 / 1	3 (100)	1 / 8
			3 (100) [a]	2.5 / 1		
ligand **3**	0.3 (30)	1 / 3	1 (48)	8 / 1	5 (80)	2 / 1

a) mol ratio **15** / **16** = 1 / 5

In 50% aqueous acetonitrile the reaction rate was even faster, but the effect on the chemoselectivity was nonuniform (Table 2). With tppts **1** exclusive formation of the cross coupled product **17** was found using carbonate or equivalent amounts of triethylamine as base. On the contrary the selectivity ratio was much less pronounced with the guanidino ligands **2** and **3** that eventually differed in their preference, too. The addition of more amine gave only a marginal rate enhancement, but definitely favoured the homo-coupling reaction channel, for either of the ligands tested.

In conclusion, cationic phosphine ligands containing the hydrophilic guanidinium group can be readily prepared and are more stable towards aerial oxidation than the customary sulfonated arylphosphines. Compared to the latter, they catalyse a Heck-coupling in water under standard conditions somewhat less efficiently.

Experimental :

^{1}H, ^{13}C and ^{31}P nuclear magnetic resonance spectra were recorded using Bruker AM 360, AC 250 and AC 200 spectrometers with internal (TMS, solvent signal) or external (^{31}P δ (H_3PO_4) = 0 ppm) standard. NMR multiplicities are abbreviated as follows : s = singlet, d = doublet, t = triplet, q = quartet, qin = quintet, m = multiplet and b = broad. Infrared spectra were recorded as neat films or KBr pills using a Perkin Elmer FTIR 1600. Melting points were determined using a Büchi , Model 150 apparatus and are uncorrected. Fast atom bombardement (FAB) mass spectra were recorded using a Varian , Model Mat CH 5. HPLC was performed on Kontron HPLC-PUMP 420, Gradient former 425 and Uvikon 720 LC Micro instruments with 250x4 Nucleosil RP 18 5µm columns. The eluents contained 30 mM H_3PO_4 and 30 mM $NaClO_4$ in addition to the organic modifier given with the individual compounds. All solvents were distilled prior to use and all reactions were carried out under nitrogen.

Phenylphosphine, diphenylphosphine, triphenylphosphine, 3-chloropropylamine, 4-iodobenzoic acid, acrylonitrile and Pd-acetate were supplied by commercial sources and used without further purification. 1H-pyrazole-1-carboxamidinehydrochloride **8**[11] and p-carboxyphenylacetylene **15**[15] were prepared using the known procedures. Compounds **7**[12,14], **11**[13] and **13**[10] were obtained by slight modifications of published procedures.

2-Cyanoethyldiphenylphosphine (11)

Freshly distilled acrylonitrile **10** (1.2 g, 22.6 mmol) was added slowly to a stirred mixture of 2.5 g (13.4 mmol) of diphenylphosphine (**9**), 0.1 ml of 50% aqueous NaOH and 5 ml of acetonitrile. After complete addition the solution was stirred for 1 h at 55 °C. The yellow solution was extracted with brine (3 x 7 ml) and the organic layer was dried with Na_2SO_4. After removal of the solvent under normal pressure the residue, a yellow oil, was distilled at 0.02 mm Hg/ 220 °C (Kugelrohr) to yield 2.7 g (11.3 mmol, 84 %) of **11** as a colourless oil, which crystallized on storage. ^{1}H-NMR (250 MHz, $CDCl_3$): δ = 2.34 (s, 2H), 2.38 (s, 2H), 7.34-7.45 (m, 10H); ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 14.1 (d, J=23 Hz, CH_2), 24.2 (d, J=14 Hz, CH_2), 119.5 (s, CN), 128.9 (d, J=7 Hz, CH), 129.5 (s, CH), 132.7 (d, J=20 Hz, CH), 136.3 (d, J=12 Hz, C); ^{31}P-NMR (101.3 MHz, $CDCl_3$): δ = -15.2; IR(KBr): ν=3050.0 w, 2255.1 w, 1481.9 m, 1432.6 s , 1308.8 w, 1188.8 w, 1099.8 w, 751.2 s, 733.6 s, 706 s.

3-Aminopropyldiphenylphosphine (7)

A) 42 ml (42 mmol) of 1 M $LiAlH_4$ in diethylether was cooled to 0 °C with stirring under N_2 and a solution of 1 g (4.2 mmmol) of **11** in 50 ml ether was added. Then the mixture was warmed to r.t. and allowed to stand for 2 d. After cooling to 0 °C 2 ml degased H_2O, 2 ml 10 % NaOH and 0.5 ml degased H_2O were added successively. The resulting precipitate was filtered and the organic layer was dried with Na_2SO_4. The product **7** (700 mg, 2.9 mmol, 69 %) was obtained after evaporation of the solvent.

B) A solution containing 65 g (0.247 mol) of triphenylphosphine **4** and 13 g (0.565 mol) of sodium in liquid ammonia (300 ml) was stirred for 3h at -78 °C. The colour changed from blue to orange. To this

solution 32.5 g (0.25 mol) of 3-chloropropylamine **6** and 300 ml of THF were added in small portions. After stirring for 2h the ammonia was allowed to evaporate slowly. The resulting yellow solution was refluxed for 8h. The solvent was evaporated and the residue was distilled (0.02 mm Hg/180-200 °C, Kugelrohr) to yield 40 g (0.164 mol, 67%) of **7**, as a pale yellow viscous liquid. ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.23 (br, 2H), 1.55 (m, 2H), 2.05 (m, 2H), 2.75 (t, J=7 Hz, 2H), 7.25-7.45 (m, 10H); ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 25.2 (d, J=12 Hz, CH_2), 30.0 (d, J=15 Hz, CH_2), 43.2 (d, J=14 Hz, CH_2), 128.3 (d, J=10 Hz, CH), 128.4 (s, CH), 132.6 (d, J=18 Hz, CH), 138.6 (d, J=14 Hz, C); ^{31}P-NMR (101.3 MHz, $CDCl_3$): δ = -15.4; IR(KBr): ν =3365.9 br, 3053.2 m, 2928.3 m, 1585.8 m, 1480.0 m, 1433.9 m, 1182.7 m, 1095.7 m, 741.1 s, 696.6 s.

3-Guanidinopropyldiphenylphosphine (2)

In a flask 500 mg (2 mmol) of **7** was added to a mixture of 300 mg (2mmol) of 1-H-pyrazol-1-carboxamidinehydrochloride[11], 360 µl (2mmol) of diisopropylethylamine and 1 ml of DMF. The solution was stirred for18 h at r.t. under nitrogen. After removal of all volatile liquids in vacuo, the yellow residue was purified over Sephadex SP-25 cation exchange resin to give **2** (480 mg, 1.4 mmol, 70 %) as a solid pale yellow residue, after washing with water and elution with 1M NH_4Ac in 50% CH_3OH / 50% H_2O. The corresponding phosphine oxide was obtained on hydrolysis with air-saturated water. ^{1}H-NMR (360 MHz, D_2O, CD_3CN): acetate salt δ = 1.67 (m, 2H), 2.13 (m 2H), 3.19 (m, 2H), 7.36-7.76 (m, 10H); ^{13}C-NMR (90.5 MHz, D_2O/CD_3CN) : acetate salt δ = 24.1 (d, J=10 Hz, CH_2), 25.3 (d, J=17 Hz, CH_2), 41.7 (d, J=14 Hz, CH_2),129.5 (d, J=19 Hz, CH), 129.4 (s, CH), 132.9 (d, J=17 Hz, CH), 138.6 (d, J=12 Hz, C), 157.3 (s, C);. ^{31}P-NMR (101.3 MHz, CD_3OD): acetate salt δ = -12.0; **2**-oxide: FAB-MS (TG) m/z = 302 (M^+,100%).

Bis(2-cyanoethyl)phenylphosphine (13)

To a mixture of 1.5 g (13.6 mmol) of phenylphosphine and 300 µl of 10 N aqueous KOH in 1.5 ml of acetonitrile 1.7 g (32 mmol) of freshly distilled acrylonitrile was added slowly at 5 °C (Caution! induction period of an exothermic reaction). The solution was stirred for another 2.5 h at r.t. and then extracted with brine (3x3 ml). The organic layer was dried with Na_2SO_4. After evaporation of the solvent the residue was distilled at 0.05 mm Hg/210-220°C (Kugelrohr) to yield 1.7 g (7.9 mmol, 58%) of **13**. ^{1}H-NMR (200 MHz, $CDCl_3$) : δ = 2.10 (m, 4H), 2.35 (m, 4H), 7.3-7.53 (m, 5H); ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 14.1 (d, J=22 Hz, CH_2), 23.9 (d, J=14 Hz, CH_2), 119.1 (d, J=13 Hz, CN), 129.1 (d, J=8 Hz, CH), 130.6 (s, CH), 132.6 (d, J=22 Hz, CH), 135.8 (d, J=20 Hz, C); ^{31}P-NMR (101.3 MHz, $CDCl_3$): δ = -22.6.

Bis(3-aminopropyl)phenylphosphine (14)

The preparation was carried out in the same way as described for the monoalkylated phosphine **7**.

Yield: 1.3 g (5.8 mmol, 75 %) of **14**. ^{1}H-NMR (200 MHz, $CDCl_3$) : δ = 1.42-1.75 (m+br, 12H), 2.70 (t, J=7 Hz, 4H), 7.32-7.55 (m, 5H); ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ =2 5.3 (d, J=12 Hz, CH_2), 29.9 (d, J=14 Hz, CH_2), 43.0 (d, J=12 Hz, CH_2), 128.3(d, J=7 Hz, CH), 128.7 (s, CH), 132.2 (d, J=19 Hz, CH), 138.3 (d, J=12 Hz, C); ^{31}P-NMR (101.3 MHz, $CDCl_3$): δ = -20.6.

Bis(3-guanidinopropyl)phenylphosphine (3)

The preparation followed the protocol for **2**. Purification on Sephadex SP-25 cation exchange polymer with a gradient of 1M NH_4Ac →2M NH_4Ac in H_2O yielded 220 mg (0.534 mmol, 60%) of **3** as a yellow viscous oil. The corresponding phosphine oxide was obtained by hydrolysis with air-saturated water. ^{1}H-NMR (360 MHz, D_2O): acetate salt δ = 2.0 (m, 8H), 3.26 (m 4H), 7.56-7.84 (m, 5H) ; ^{13}C-NMR (90.5 MHz, D_2O/CD_3CN) : acetate salt δ = 24.4 (d, J=8 Hz, CH_2), 25.4 (d, J=13 Hz, CH_2), 42.1 (d, J=14 Hz, CH_2),

130.0 (d, J=12 Hz, CH), 130.6 (s, CH), 133.4 (d, J=18 Hz, CH), 136.7 (d, J=10 Hz, C), 157.2 (s, C) ; ^{31}P-NMR (101.3 MHz, CD_3OD): acetate salt δ = -21.2 ; **3**-oxide: FAB-MS(TG) m/z = 325 (M+, 100%).

General procedure for Heck coupling reactions:

The catalyst stock solution was prepared from Pd-acetate (100 µmol) and ligand (500 µmol) in 10 ml degased water. After addition the solution was stirred at room temperature for 1h and kept as homogeneous solution under nitrogen in a refrigerator.

Equimolar amounts of 4-iodobenzoic acid (10 µmol) **(16)** and p-carboxyphenylacetylene **(15)** were dissolved in 1 ml of solvent (water or water/acetonitrile 1:1). Then the base (2-5 eq) was added and the mixture was stirred at 50 °C under nitrogen. After the solution became homogeneous (≈5 min) 5 mol% Pd-catalyst stock solution and 10 mol% CuI (in CH_3CN) were added. The composition of the reaction mixture was quantitatively monitored by gradient HPLC with the addition of catalyst as start. Coupling products were identified in the otherwise clean chromatogramms by comparison with independently synthesized authentic material.

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