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2-Pyrimidylphosphines: A New Class of Ligands for Transition Metal Catalysis

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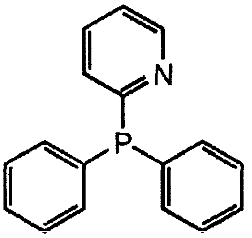
Abstract: The synthesis of 2-pyrimidyldiphenylphosphine (**2**), bis-2-pyrimidylphenylphosphine (**3**) and tris-2-pyrimidylphosphine (**4**) is described. Ligand **2** forms cationic complexes with palladium(II) in which four-membered P/N-chelates are involved, leading to a very active catalyst for the carbonylation of alkynes. © 1998 Elsevier Science Ltd. All rights reserved.

Although triphenylphosphine is known to serve as the standard ligand for a wide variety of transition metal catalyzed reactions,[1] it is not well suited for a significant number of organic transformations. In such cases phosphines having different electronic and/or steric properties have been developed, tris-2-furanylphosphine[2] and 2-pyridyldiphenylphosphine (**1**)[3] being two prominent examples. The Shell process for the carbonylation of propyne with formation of methacrylic acid ester is based on cationic Pd catalysts stabilized by **1** under acidic conditions, labile four-membered P/N-chelates of palladium being the proposed (but never proven) catalytic intermediates.[3a-b] In this communication we describe the synthesis of the 2-pyrimidylphosphines **2**, **3** and **4** as well as initial observations regarding their use as ligands in some Pd-catalyzed transformations.



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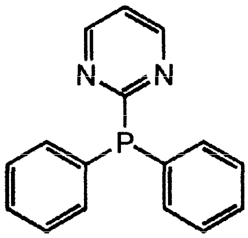

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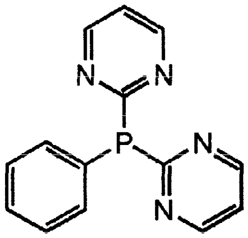

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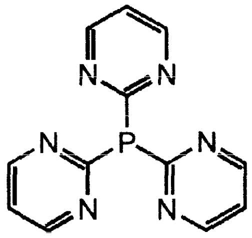

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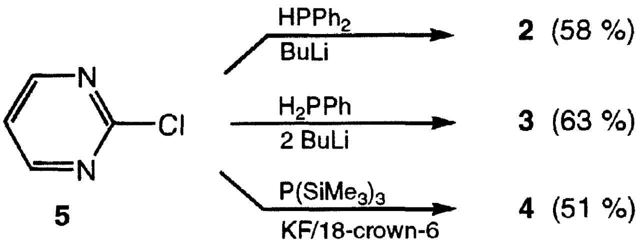
The starting material in all three syntheses was chosen to be commercially available 2-chloropyrimidine **5**, as shown below.[4] The phosphines **2**,[5] **3** and **4** were characterized by standard methods, including ^{31}P NMR spectroscopy (δ = 4.1, 8.9 and 14.6 ppm, respectively, compared to -5.6 ppm for PPh_3) and by X-ray crystallography, which shows no significant geometric changes relative to PPh_3.[4a] Thus, primarily electronic effects (electron withdrawing), the possibility of P/N coordination and/or N protonation are to be expected of ligands **2**-**4** in relevant cases.



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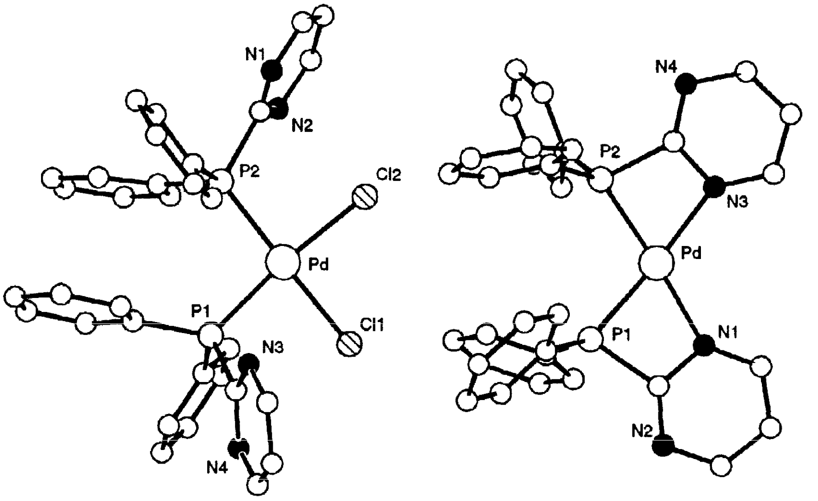
Various Pd complexes of the phosphines were prepared, e. g., those based on the ligand **2**. Whereas the crystal structure of the $PdCl_2$ adduct **6**[6] reveals only Pd-P coordination, that of the cationic complex **7**[7] involves *two* four-membered palladacycles based on P/N coordination (Fig. 1). In light of these observations, Drent's postulate [3a-b] of similar complexes based on P/N coordination of the analogous pyridylphosphine **1** seems quite reasonable.

$$\mathbf{2} \xrightarrow{(PhCN)_2PdCl_2} \underset{\mathbf{6}}{[(C_4N_2H_3)(C_6H_5)_2P]_2PdCl_2} \xrightarrow{AgBF_4} \underset{\mathbf{7}}{[(C_4N_2H_3)(C_6H_5)_2]_2Pd^{2+}\,[BF_4]^-_2}$$

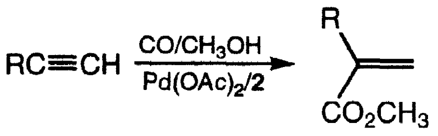


a) b)

Fig. 1. Crystal structures of a) **6** (P1-Pd-P2 97.71(2)°) and b) **7** (dication, P1-Pd-P2 105.48(3), N1-Pd-N3 113.0(1), P1-Pd-N1 70.8(1), P2-Pd-N3 70.6(1)°)

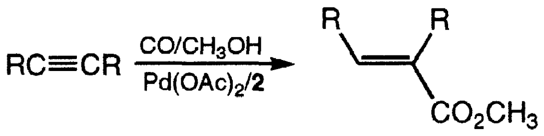
We first tested the ligands **2-4** in a standard Heck reaction involving bromobenzene and styrene. Using 1 mol-% $Pd(OAc)_2$ and 5 mol-% of a ligand in *N*-methylpyrrolidone as solvent and NaOAc as base (130 °C/6 h), rather different results were obtained, depending upon the nature of the ligand. In the case of **2**, 80 % of *E*-stilbene was obtained, similar to the use of PPh_3. However, upon using **3** and **4**, the yield dropped to 48 % and 3 %, respectively, showing that the increasing electron-withdrawing effect of the pyrimidyl moieties is detrimental to the Heck reaction.

Pronounced ligand effects were also observed in the carbonylation of alkynes[3a-b,8] (e. g., **8a**→**9a**). Using only 0.057 mol-% $Pd(OAc)_2$ and an excess of phosphine in the presence of CH_3OH containing some CH_3SO_3H,[3a-b] conversion to **9a** after 2 h varied drastically according to the nature of the ligand:[9] PPh_3 (14 %); **2** (> 97 %); **3** (70 %); **4** (2 %, after 17 h: 29 %). Thus, compound **2** is the ligand of choice. A TOF of 7000 h^{-1} was easily achieved. The system is at least as active as the one based on **1**[4a]. It is therefore very probable that under the acidic conditions P/N-chelates of palladium as well as protonated pyrimidyl moieties are involved (which intramolecularly deliver protons onto the vinyl-palladium intermediate in the last stage of the catalytic cycle, similar to the proposed mechanism in the case of ligand **1**).[3a-b] If the ligand contains too many electron-withdrawing pyrimidyl residues, the proper balance of electron effects is disturbed adversely.



8 a) R = n-C_4H_9	**9 a**) > 97 %
b) R = t-C_4H_9	**b**) 83 %
c) R = C_6H_5	**c**) > 97 %
d) R = $Si(CH_3)_3$	**d**) 25 %

Internal alkynes **10** can also be carbonylated,[8] the results being comparable or better than those obtained in other catalytic systems.[9]



10 a) R = C_6H_5	**11 a**) 97 %
b) R = C_2H_5	**b**) 48 %

In summary, the 2-pyrimidylphosphine **2** is an excellent ligand for the Pd-catalyzed carbonylation of alkynes. An X-ray structural analysis has identified for the first time intermediate cationic four-membered chelates based on P/N complexation which are relevant in these catalytic reactions.

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4. a) Demuth, R. Dissertation, Universität Köln, 1998. b) Synthesis of **2**: In a Schlenk tube (under Ar) a solution of diphenylphosphine (8.7 ml, 50 mmol) in dry THF (35 ml) is cooled to -18 °C and treated dropwise with 31.2 ml of a 1.6 M solution of *n*-butyllithium in hexane (50 mmol). After stirring for 1 h, 2-chloropyrimidine **5** (5.7 g, 50 mmol) is slowly added. Following removal of the cooling bath, stirring is continued for 4 h, followed by the addition of H_2O (50 ml) and two extractions with ethyl acetate (30 ml). The solvent is removed and the residue crystallized from CH_3OH/CH_2Cl_2 (5:1), resulting in colorless crystals of **2** (7.6 g, 58 %); mp 128 °C.
5. During our work another group has reported the synthesis of **2**: Li, S.; Zhang, Z.-Z.; Mak, T. C. W. *J. Organomet. Chem.* **1997**, *536-537*, 73-86.
6. X-ray analysis of **6**: $C_{32}H_{26}Cl_2N_4P_2Pd\cdot CH_4O$, M_r = 737.85 g mol^{-1}, yellow prism, crystal size 0.25 × 0.28 × 0.39 mm, monoclinic, $P2_1/n$ [No. 14], a = 10.902(1), b = 18.501(2), c = 16.528(2) Å, β = 107.14(1)°, V = 3185.4(7) Å^3, T = 293 K, Z = 4, d_{cal} = 1.54 g cm^{-3}, μ = 0.89 mm^{-1}, Enraf-Nonius CAD4 diffractometer, λ = 0.71069 Å, ω-2θ-scan, 7261 independent reflections, 5823 observed $[I > 2\sigma(I)]$, $[(\sin\theta)/\lambda]_{max}$ = 0.65 Å^{-1}, no absorption correction, direct methods (SHELXS-97, Sheldrick, G. M. *Acta Cryst.* **1990**, *A46*, 467-473), least-squares refinement (on F_o^2, SHELXL-97, Sheldrick, G. M., University of Göttingen, 1997), H riding, methanol of crystallization disordered (50:50), 386 refined parameters, R_1 = 0.031 (obs. data), wR_2 = 0.079 (Chebyshev weights), final shift/error 0.001, residual electron density +0.629 eÅ^{-3}.
7. X-ray analysis of **7**: $C_{32}H_{26}B_2F_8N_4P_2Pd\cdot 0.25O$, M_r = 812.5 g mol^{-1}, orange plate, crystal size 0.07 × 0.37 × 0.40 mm, monoclinic, $P2/a$ [No. 13], a = 15.649(2), b = 13.087(1), c = 16.840(1) Å, β = 103.72(1)°, V = 3350.4(5) Å^3, T = 100 K, Z = 4, d_{cal} = 1.61 g cm^{-3}, μ = 0.73 mm^{-1}, Enraf-Nonius CAD4 diffractometer, λ = 0.71069 Å, ω-2θ-scan, 7555 independent reflections, 5628 observed $[I > 2\sigma(I)]$, $[(\sin\theta)/\lambda]_{max}$ = 0.65 Å^{-1}, analytical absorption correction (T_{min} 0.7953, T_{max} 0.9507), direct methods (SHELXS-97, Sheldrick, G. M. *Acta Cryst.* **1990**, *A46*, 467-473), least-squares refinement (on F_o^2, SHELXL-97, Sheldrick, G. M., University of Göttingen, 1997), H riding, solvent of crystallization (O, refined occupancy 0.25), 447 refined parameters, R_1 = 0.040 (obs. data), wR_2 = 0.101 (Chebyshev weights), final shift/error 0.001, residual electron density +1.391 eÅ^{-3} (1.04 Å from F6). Atomic coordinates and e.s.d.'s for both crystal structures (**6** and **7**) have been deposited at the Cambridge Crystallographic Data Centre.
8. General procedure for the carbonylation of alkynes:[4a] An autoclave is charged with methanol (30 ml), *N*-methylpyrrolidone (10 ml), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), ligand **2** (264.3 mg, 1 mmol), methanesulfonic acid (2.3 mmol) and 1-hexyne (43.5 mmol). It is filled with CO (60 bar) and heated to 60 °C for 2 h. In the case of sterically hindered substrates such as **8b**, 0.31 mol-% of $Pd(OAc)_2$ is used. Thereafter the autoclave is cooled to room temp., and the contents is filtered through SiO_2 prior to analysis by gas chromatography.
9. Other catalysts in carbonylation reactions of alkynes: a) Reppe, W. *Justus Liebigs Ann. Chem.* **1953**, *582*, 1-37. b) Zargarian, D.; Alper, H. *Organometallics* **1993**, *12*, 712-724. c) Itoh, K.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1992**, *33*, 5369-5372. d) Monteiro, A. L.; Lando, V. R.; Gasparini, V. *Synth. Commun.* **1997**, *27*, 3605-3611.