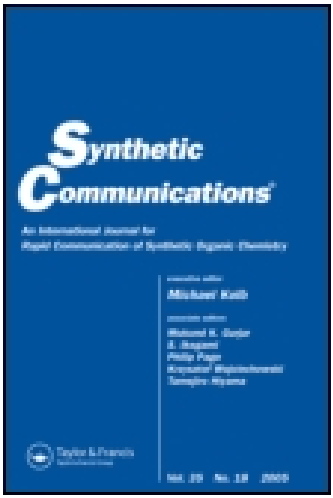

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A New Palladium-Catalyzed P-C Coupling Reaction: Synthesis of Triarylphosphine Oxides and Diarylmethylphosphine Oxides

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A NEW PALLADIUM-CATALYZED P-C COUPLING REACTION: SYNTHESIS OF TRIARYLPHOSPHINE OXIDES AND DIARYLMETHYLPHOSPHINE OXIDES

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Abstract: The first palladium-catalyzed P-C coupling reaction of aryl halides with (hydroxymethyl)phosphines is described. Hydroxymethylphosphines act as cheap and easy to use H_3PO and $CH_3P(O)H_2$ equivalents. Tertiary diarylmethylphosphine oxides **5** and triarylphosphine oxides **6** are accessible in a one pot reaction in overall yields between 45-60%.

The refinement of aryl halides by palladium-catalyzed coupling reactions is one of the most active areas in homogeneous catalysis. In this respect palladium-catalyzed C-N bond forming reactions have recently emerged as a useful synthetic tool for the preparation of aryl amines.[1] However, only few reports of analogous P-C cross coupling reactions are known.[2-5] As an example Stelzer and co-workers described the reaction of secondary phosphines or phosphine oxides with aryl bromides and iodides to provide aryl phosphines and phosphine oxides, respectively.[2] The synthetic value of the P-C coupling reactions to organic

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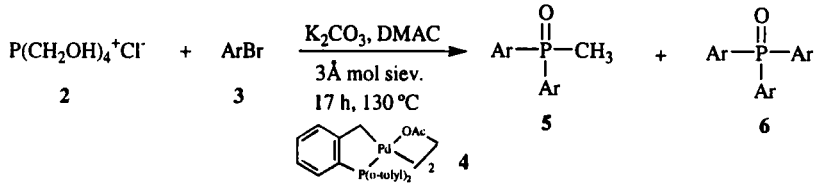
synthesis could be considerably enhanced if the range of starting materials is expanded to simple phosphorus precursors, such as PH_3 or $AlkylPH_2$. However, these compounds are often highly toxic gases that are difficult to handle. Accordingly, we examined the possibility of using easily available equivalents of P-H bonds for P-C coupling reactions. In this paper we report our preliminary results for the preparation of methyldiarylphosphine oxides and triarylphosphine oxides starting from trishydroxymethylphosphine **1** or tetrakis(hydroxymethyl)phosphonium chloride **2**, which are easy to handle and commercially available.[6]

As a model reaction, the coupling of 4-bromofluorobenzene **3a** with tetrakis(hydroxymethyl)phosphonium chloride **2**, a precursor to **1** in the presence of base, was studied using a standard set of conditions (dimethylacetamide, 10 eq. K_2CO_3, 3 mol% palladacycle **4**,[7] 17 h, 3Å mol siev.). When 5 equivalents of **3a** and **2** were combined and heated to 130 °C for 17 h in a closed reaction vessel, two P-C coupling products bis(4-fluorophenyl)methylphosphine oxide **5a** and tris(4-fluorophenyl)phosphine oxide **6a** are formed in 13 and 23% yields, respectively. No other major products were observed by GC.

In order to facilitate the loss of $H_2C{=}O$ from **2** and to increase the yield of the coupling products, the reaction of **3a** and **2** was repeated whereby a gentle stream of nitrogen was passed over the reaction solution. Indeed, the overall yield of P-C coupling products increased from 36 to 49%. Surprisingly, the **5a/6a** selectivity changed dramatically. Here, diarylmethylphosphine oxide **5a** and triarylphosphine oxide **6a** formed in 38 and 11% yields, respectively. The same product selectivity and yields were obtained when tris(hydroxymethyl)phosphine **1**[8] was employed instead of **2** under similar reaction conditions (run 3, Scheme 1). Hence, **2** is a precursor to **1** under the reaction conditions. When this reaction was repeated without the N_2 stream, but still in an open reaction vessel, the yield of P-C coupling products increased slightly up to 53% (run 4). A ^{31}P NMR spectra of the

Table 1. Palladium-catalyzed P-C coupling reaction



run	compound	Ar	ratio of 2/3	yield of P-C coupling products (%)[a]	selectivity (5/6)[a]
1	**3a**		1/5	36[b]	36:64
2	**3a**		1/5	49[c]	78:22
3	**3a**	F—	1/5	40[d]	83:17
4	**3a**		1/5	61	81:19
5	**3a**		5/1	<5	<1:99
6	**3b**		1/5	54	87:13
7	**3b**	Cl—	5/1	<5	<1:99
8	**3c**		1/5	58	81:19
9	**3c**	H_3C—	5/1	<5	<1:99
10	**3d**		1/5	53	72:28
11	**3d**	H_3CO	5/1	<5	<1:99

[a]determined by GC using diethyleneglycol dibutylether as an internal standard. [b]reaction performed in closed vessel. [c]gentle stream of N_2 passed over top of reaction. [d]$P(CH_2OH)_3$ employed as starting material instead of **2**.

crude product reaction mixture of run 3 indicated that the phosphorus containing precursors **2** and **1** were completely consumed.

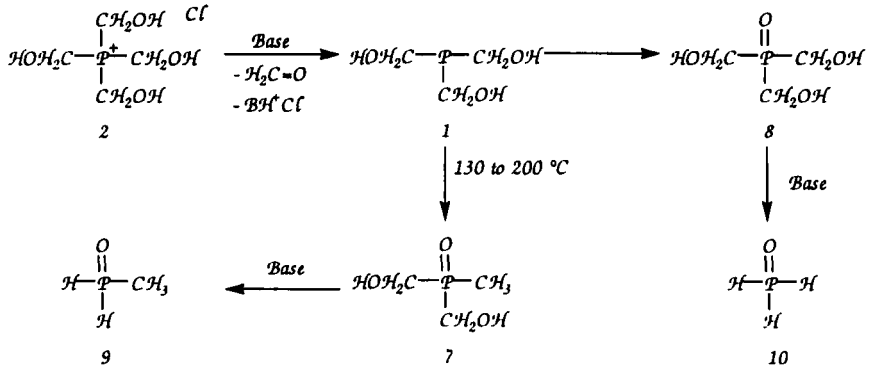
Apart from **5a** and **6a**, no other phosphorus containing products were observed. Applying a five fold excess of phosphine salt **2** for the reaction with **3a** only traces of triarylphosphine oxide **6a** were found by GC.

For reactivity comparison, 4-chlorobromobenzene **3b**, 4-methylbromobenzene **3c**, and 6-methoxy-2-bromo-naphthalene **3d** were also reacted with phosphine salt **2** under standard catalytic conditions (i.e. reflux condenser attached to oil bubbler, five fold excess ArBr). As shown in Table 1, methylphosphine oxide **5b-d** and

triarylphosphine oxide **6b-d** formed in overall yields of 45-60% yield. Seletivities for **5** were in the range of 75-85%. On the other hand only traces of **6b-d** were observed when **3b-d** were combined with excess **2** under catalytic conditions.

The rearrangement of tris(hydroxymethyl)phoshine **1** to bis(hydroxymethyl)-methylphosphine oxide **7** occurs only at temperatures greater than 130 °C (Scheme 1). Catalysis does not occur below 130 °C. Hence, the rate determining step of this new domino P-C coupling process for the formation of **5** is believed to be the *in situ* generation of **7**.

Scheme 1. Rearrangement of **1** to **9** and **10**.



In order to prove whether **7** and **8** are precursors to the P-C coupling products **5** and **6** we prepared a 57/43 mixture of **7/8** according to patent literature[9] and combined this mixture with **3a** using the standard catalytic conditions. The formation of **6a**, albeit in small yields, indicated that tris(hydroxymethyl)phosphine oxide **8** is indeed a precursor to **6a**.

In conclusion, we have developed a new domino sequence involving P-C coupling reactions. Both methyldiarylphosphine- and triarylphosphine oxides can be prepared starting from inexpensive tetrakis(hydroxymethyl)phosphonium chloride **2** or tris(hydroxymethyl)phosphine **1**. **1** and **2** are clearly superior

reagents compared to the corresponding PH derivatives regarding price and handling. Activated and deactivated aromatic bromides can be employed in this P-C coupling reaction. Although the yields of methyldiarylphosphine oxides **5** were so far only moderate, it must be considered that at least 5 reaction steps are taking place in this new domino sequence (rearrangement of **1** to **7**, two times loss of $H_2C{=}O$, and two times coupling of the „PH" species with ArBr). It is worthwhile mentioning that compounds of type **5** are of general interest as flame retardants, agrochemicals, and surfactants.[10] In addition, special derivatives might be of importance as precursors to new ligands.

Experimental

General Data. Instrumental protocols and solvent and reagent purifications were identical to those in earlier papers.[11] Diethyleneglycol-dibutylether was used as an internal standard for GC experiments. Reagents were purchased from common commercial sources. NMR spectra were recorded at ambient probe temperature and referenced as follows: ^1H (ppm) $Si(CH_3)_4$; $^{13}C\{^1H\}$ (ppm) $CDCl_3$ (77.0); ^{31}P (ppm), external 85% H_3PO_4 (0.00). All coupling constants (J) are in Hz.

Reaction of $P(CH_2OH)_4^+Cl^-$ (2) and FC_6H_4Br (3a). A Schlenk flask was charged with phosphapalladacycle (**4**, 0.060 g, 0.13 mmol, 3.0 mol %),[11] tetrakis(hydroxymethyl)phosphonium chloride (**2**, 0.820 g, 4.31 mmol), 3Å molecular sieves (0.60 g), and *N*,*N*-dimethylacetamide (8 mL). Then 4-fluorobromobenzene (**3a**, 2.36 mL, 21.5 mmol) and potassium carbonate (5.96 g, 43.1 mmol) were added. A reflux condenser connected to an oil bubbler was attached and the flask was heated for 17 h at 130 °C. The flask was cooled to room temperature and 5% HCl solution was added until gas evolution ceased (30 mL). The mixture was filtered through Celite and washed with CH_2Cl_2 (100 mL).

The organic phase was collected and the aqueous phase was washed with CH_2Cl_2 (3 x 50 mL). Solvent was removed from the combined organic fractions via rotary evaporation. Column chromatography (hexane/ethylacetate =1/10) of the residue yielded tris(4-fluorophenyl)phosphine oxide (**6a**, 0.14 g, 0.43 mmol, 10%)[12] and bis(4-fluorophenyl)methylphosphine oxide (**5a**, 0.43 g, 1.72 mmol, 40%)[13] as tan powders. IR (cm^{-1}, KBr): ν(P=O) 1180 (s). MS (*m/z*): 252 (M^+), 237 (M^+ - CH_3).

NMR (**5a**, $CDCl_3$): ^1H (δ), 7.70 (ddd, $^4J_{HF}$ = 5.5, $^3J_{HH}$ = 8.5, $^3J_{HP}$ = 11.5, 4H of *o*-PC_6H_4), 7.15 (td, $^4J_{HP}$ = 2.0, $^3J_{HF,HH}$ = 8.5, 4H of *m*-PC_6H_4), 2.00 (d, $^2J_{HP}$ = 13.5, CH_3); $^{13}C\{^1H\}$ (ppm) 164.9 (dd, $^1J_{CF}$ = 254, $^4J_{CP}$= 2.9, *p*-PC_6H_4), 132.9 (dd, $^3J_{CF}$ = 8.8, $^2J_{CP}$= 10.7, *o*-PC_6H_4), 129.7 (dd, $^4J_{CF}$ = 3, $^1J_{CP}$ = 105, *i*-C_6H_4), 116.1 (dd, $^2J_{CF}$ = 21.4, $^3J_{CP}$ = 12.6, *m*-PC_6H_4), 16.8 (d, $^1J_{CP}$ = 74.9, CH_3); $^{31}P\{^1H\}$(ppm) 32.8 (s, CD_3OD), 28.1 (s, $CDCl_3$).

Reaction of $P(CH_2OH)_4^+Cl^-$ (2) and ClC_6H_4Br (3b). Phosphapalladacycle (**4**, 0.030 g, 0.063 mmol, 3.0 mol %),[11] $P(CH_2OH)_4^+Cl^-$ (**2**, 0.40 g, 2.1 mmol), 3Å molecular sieves (0.50 g), *N*,*N*-dimethylacetamide (10 mL), ClC_6H_4Br (**3b**, 2.01 g, 10.5 mmol) and K_2CO_3 (2.90 g, 21.0 mmol) were combined as described above for the reaction of $P(CH_2OH)_4^+Cl^-$ and FC_6H_4Br. A similar workup and chromatography (methanol/CH_2Cl_2 = 1/30) yielded tris(4-chlorophenyl)phosphine oxide (**6b**, 0.031 g, 0.084 mmol, 4%)[14] and bis(4-chlorophenyl)methylphosphine oxide (**5b**, 0.209 g, 0.733 mmol, 35%)[15] as tan powders. IR (cm^{-1}, KBr): ν(P=O) 1180 (s). MS (*m/z*): 285 (M^+), 260 (M^+ - CH_3).

NMR (**5b**, $CDCl_3$): ^1H (δ) 7.63 (dd, $^3J_{HH}$ = 8.5, $^3J_{HP}$ = 11.5, 4H of *o*-PC_6H_4), 7.45 (dd, $^4J_{HP}$ = 2.0, $^3J_{HH}$ = 8.5, 4H of *m*-PC_6H_4), 2.01 (d, $^2J_{HP}$ = 13.1, CH_3); $^{13}C\{^1H\}$ (ppm) 138.5 (d, $^4J_{CP}$ = 2.9, *p*-PC_6H_4), 132.0 (d, $^1J_{CP}$ = 102, *i*-PC_6H_4), 131.8 (d, $^2J_{CP}$ = 10.7, *o*-PC_6H_4), 129.0 (d, $^3J_{CP}$ = 12.6, *m*-PC_6H_4), 16.4 (d, $^1J_{CP}$ = 73.9, CH_3); $^{31}P\{^1H\}$ (ppm): 28.2 (s).

Reaction of $P(CH_2OH)_4^+Cl^-$ (2) and $H_3CC_6H_4Br$ (3c). Phosphapalladacycle (**4**, 0.047 g, 0.10 mmol, 3.0 mol %),[11] $P(CH_2OH)_4^+Cl^-$ (**2**, 0.640 g, 3.36 mmol), 3Å

molecular sieves (0.50 g), *N*,*N*-dimethylacetamide (10 mL), $H_3CC_6H_4Br$ (2.87 g, 16.8 mmol) and K_2CO_3 (4.60 g, 33.6 mmol) were combined as described above for the reaction of $P(CH_2OH)_4^+Cl^-$ and FC_6H_4Br. A similar workup and chromatography (methanol/CH_2Cl_2 = 1/30) yielded tris(4-tolyl)phosphine oxide (**6c**, 0.100 g, 0.312 mmol, 9%)[14] and bis(4-tolyl)methylphosphine oxide (**5c**, 0.360 g, 1.48 mmol, 44%)[15] as tan powders. IR (cm^{-1}, KBr): ν(P=O) 1179 (s). MS (*m/z*): 244 (M^+), 229 ($M^+ - CH_3$).

NMR (**5c**, $CDCl_3$): ^1H (δ) 7.61 (dd, $^3J_{HH}$ = 8, $^3J_{HP}$ = 12, 4H of *o*-PC_6H_4), 7.26 (d, $^3J_{HH}$ = 8, 4H of *m*-PC_6H_4), 2.39 (s, 6H of $2CH_3$), 1.98 (d, $^2J_{HP}$ = 13.1, CH_3); $^{13}C\{^1H\}$ (ppm) 142.0 (d, $^4J_{CP}$ = 2.9, *p*-PC_6H_4), 131.0 (d, $^1J_{CP}$ = 104, *i*-PC_6H_4), 130.5 (d, $^2J_{CP}$ = 9.7, *o*-PC_6H_4), 129.3 (d, $^3J_{CP}$ = 11.7, *m*-PC_6H_4), 21.5 (s, CCH_3), 16.7 (d, $^1J_{CP}$ = 72.9, CH_3); $^{31}P\{^1H\}$ (ppm) 29.3 (s).

Reaction of $P(CH_2OH)_4^+Cl^-$ (2) and 6-methoxy-2-bromonaphthaline (3d). Phosphapalladacycle (**4**, 0.038 g, 0.080 mmol, 3.0 mol %)[11], $P(CH_2OH)_4^+Cl^-$ (**2**, 0.510 g, 2.68 mmol), 3Å molecular sieves (0.93 g), *N*,*N*-dimethylacetamide (10 mL), $H_3COC_{10}H_6Br$ (**3d**, 3.17 g, 13.4 mmol) and K_2CO_3 (3.69 g, 26.7 mmol) were combined as described above for the reaction of $P(CH_2OH)_4^+Cl^-$ and FC_6H_4Br. A similar workup and chromatography (methanol/CH_2Cl_2 = 1/15) yielded tris-2-(6-methoxynaphthyl)phosphine oxide (**6d**, 0.123 g, 0.237 mmol, 9%) and bis-2-(6-methoxynaphthyl)methylphosphineoxide (**5d**, 0.262 g, 0.714 mmol, 27%) as tan powders. IR (**5d**, cm^{-1}, KBr): ν(P=O) 1178 (s).

NMR (**6d**, $CDCl_3$): ^1H (δ) 8.26 (d, $^3J_{HP}$ = 13.6, 3H of Ar), 7.88-7.65 (m, 9H of Ar), 7.25-7.13 (m, 6H of Ar), 3.93 (s, OCH_3); $^{13}C\{^1H\}$ (ppm) 159.3 (s, $COCH_3$), 127.4 (d, $^1J_{CP}$ = 106, *i*-PC_6H_4), 127.9, 126.6 (2d, $^3J_{CP}$ = 13.6, 12.6, *m*-Ar), 133.6, 127.7, (2d, $^2J_{CP}$ = 9.7, 10.7, *o*-Ar), 136.2, 130.4, 119.7, 105.6 (4s, Ar) 55.3 (s, OCH_3); $^{31}P\{^1H\}$ (ppm) 34.3 (s, CD_3OD), 29.0 (s, $CDCl_3$).

NMR (**5d**, $CDCl_3$): ^1H (δ) 8.29 (d, $^3J_{HP}$ = 13.5, 2H of Ar), 7.87-7.71 (m, 4H of Ar), 7.67-7.59 (m, 2H of Ar), 7.19 (dd, $^4J_{HH}$ = 2.5, $^3J_{HH}$ = 9.0, 2H of Ar), 7.12 (d, $^4J_{HH}$ = 2.5, 2H of Ar), 3.92 (s, 6H of OCH_3), 2.14 (d, $^2J_{PH}$ = 13.1, PCH_3); $^{13}C\{^1H\}$

(ppm) 159.2 (s, $COCH_3$), 136.0 (d, $^4J_{CP}$ = 2.9, *p*-PAr), 128.5 (d, $^1J_{CP}$ = 104, *i*-PAr), 127.9, 127.2 (2d, $^3J_{CP}$ = 12.6, 11.7, *m*-PAr), 131.8, 126.2 (2d, $^2J_{CP}$ = 9.7, 10.7, *o*-PC_6H_4), 130.3, 119.8, 105.6 (3s, Ar), 55.3, (s, OCH_3), 16.6 (d, $^1J_{CP}$ = 73.9, PCH_3); $^{31}P\{^1H\}$ (ppm) 29.7 (s).

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