An Easily Accessible Resin-Supported Palladium Catalyst for Sonogashira Coupling

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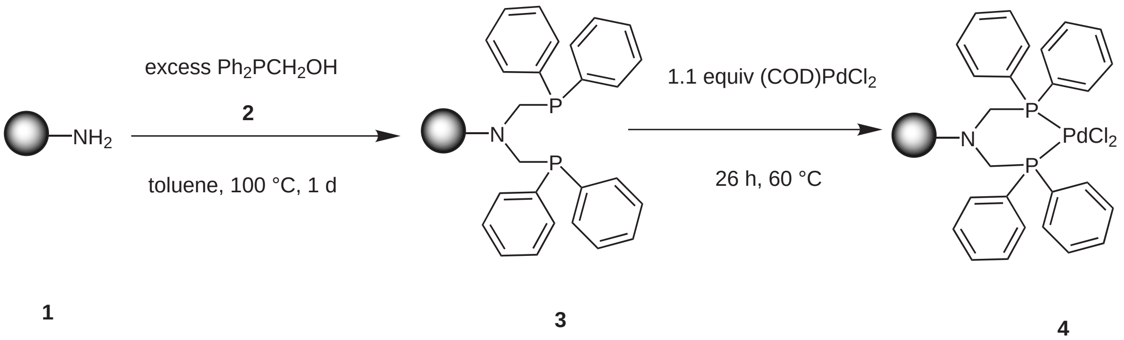
Abstract: Readily available aminomethyl-polystyrene beads can be transformed in a one-pot reaction to an air-stable polymer-bound chelate phosphine, which can be used for the immobilization of homogeneous catalysts. Such prepared Pd catalysts have proven to be useful reagents for mediating Sonogashira-coupling reactions.

Key words: combinatorial chemistry, catalyst, cross-coupling, solid-phase, palladium

Parallel combinatorial synthesis in solution using immobilized reagents, catalysts, and scavengers has emerged as a powerful technique for the preparation of diverse libraries of compounds. The groups of Ley and others have demonstrated the practicability of this approach in synthesizing complex natural products by multi-step sequences requiring many different kinds of heterogenized reagents, which can be removed by simple filtration.[1] Especially the immobilization of transition metal catalysts has attracted a lot of attention, as the high cost of these metals defines the recycling of these catalysts a desirable goal.[2] Furthermore the intrinsic toxicity of most transition metals makes the complete removal of even traces thereof an imperative for providing substances qualified for biological testing. Although many literature reports exist for the immobilization of transition metal catalysts, most of these strategies require multi-step sequences for the synthesis of the ligands. Our approach was guided by three imperatives: the polymeric reagent should be easily accessible (1), starting from inexpensive reagents (2). The ligand should be air stable at room temperature, which should allow its storage in normal bottles with unlimited shelf life (3). Over the last few years the *N*,*N*-bis(diphenylphosphinomethyl)amino-functionality has been used for the preparation of dendrimer-bound and supramolecular homogeneous catalysts.[3] Just recently insoluble versions of this chelating ligand have been applied in Rh-catalyzed hydroformylation and Ru-catalyzed hydrogenation.[4] This paper describes the simple and fast preparation of immobilized Pd-catalysts fulfilling the criteria detailed above.[5]

Bis(diphenylphosphinomethyl)aminomethylpolystyrene (**3**) can be easily synthesized by heating readily available aminomethyl polystyrene (**1**) (Novabiochem 01-64-0010, 1% cross-linking, 200-400 mesh, 1.13 mmol/g loading) with an excess of diphenylphosphinomethanol (**2**), which resulted from adduct formation between diphenylphosphine and paraformaldehyde (Scheme 1).[6] The identity of the resin bound phosphine was confirmed by gel phase ^{31}P NMR, which revealed a single peak at $\delta = -27$ ppm, in perfect agreement with the values reported for homogeneous analogues of this ligand.[3] Elemental analysis revealed that the modification of **1** has been carried out in quantitative yield. In order to investigate its stability, resin **3** was stored at room temperature under air. After six months this sample was subjected again to gel phase ^{31}P NMR. Additional formation of P(V)-species was not detectable, which convincingly demonstrates the high stability of these resin-bound bidentate ligands. After having secured the identity of these ligands we explored its potential for the preparation of transition metal catalysts. Palladium catalyst **4** was prepared by ligand metathesis



Scheme 1 Synthesis of resin-bound Pd catalyst **4**

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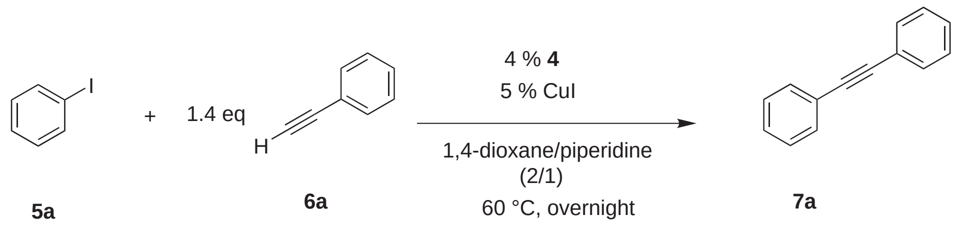

Run 1:	99 % yield
Run 2:	99 % yield
Run 3:	99 % yield
Run 4:	99 % yield

Scheme 2 Recycling experiments in the Sonogashira reaction with catalyst **4**

reaction through stirring **3** with (COD)$PdCl_2$. Quantitative incorporation of Pd could be confirmed by elemental analysis and gel phase ^{31}P NMR ($\delta = 9.2$ ppm).[7] We screened our freshly prepared catalysts in the Sonogashira-coupling of a representative set of iodoaromatics with terminal alkynes.[8] Despite the general use of this reaction in organic synthesis, solid-supported catalysts have not been widely used for this reaction yet.[9]

Using 4 mol% of catalyst **4** we investigated the catalytic activity and recyclability of our catalyst. Even after 4 runs we observed complete conversion of substrate **5a** to product **7a** overnight (Scheme 2).

Having identified the appropriate reaction conditions for the Sonogashira-reaction we investigated the scope of the reaction. We observed complete conversion for all substrates after 2 hours at 60 °C, irrespective of the electronic nature of the substituents of iodobenzenes **5a**–**e**. Only the reaction with the less reactive alkyne 1-hexyne (**6b**) required slightly longer reaction times, but also led to complete conversion of starting materials (Scheme 2, Table 1). After removal of the resin bound catalysts by filtration coupling products **7a**–**m** were isolated in very good to excellent yields (Table 1).[10] The good catalytic performance and the easy accessibility of **4** make them a highly attractive supported reagent for the parallel solution phase synthesis of combinatorial libraries.

In conclusion, we have developed a simple strategy for the preparation of Pd-catalysts bound on polymeric supports.[11] These catalysts exhibited good reactivity in the Sonogashira-coupling of iodoaromatics, which compares well to all other published results with heterogenized Pd-catalysts.[9] Additional studies on the reactivity of the resin bound Pd catalysts **4** and applications to the generation of solution phase libraries are in progress and will be the subject of future reports.

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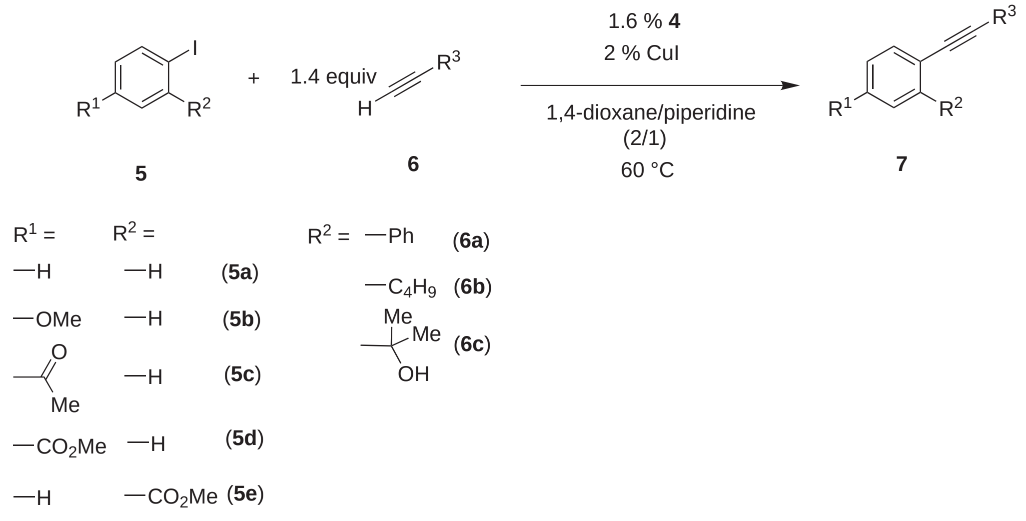

Scheme 3 Sonogashira coupling with resin-bound Pd catalyst **4**

Table 1 Sonogashira Coupling Reactions (Scheme 3)

Entry	**5**	**6**	**7**	Reaction time (h)	Conversion (%)	Isolated yield (%)
1	**5a**	**6a**	**7a**	2	>99	99
2	**5a**	**6b**	**7b**	21	>99	86[a)]
3	**5a**	**6c**	**7c**	2	>99	89
4	**5b**	**6a**	**7d**	2	>99	92
5	**5b**	**6b**	**7e**	21	>99	99
6	**5b**	**6c**	**7f**	2	>99	91
7	**5c**	**6a**	**7g**	2	>99	99
8	**5c**	**6b**	**7h**	3	>99	99
9	**5c**	**6c**	**7i**	2	>99	94
10	**5d**	**6a**	**7j**	2	>99	98
11	**5d**	**6b**	**7k**	8	>99	99
12	**5d**	**6c**	**7l**	2	>99	93
13	**5e**	**6a**	**7m**	2	>99	97

[a] Due to the volatility of this compound we were unable to isolate this compound without residual solvent. The reported yield has been calculated by subtracting residual solvent from isolated material based on the ^{1}H NMR signals.

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(5) Parallel to our work the group of Uozumi has prepared amphiphilic Pd catalysts for Suzuki- and Heck-couplings using Argogel–NH$_2$ applying a similar strategy:.
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(b) Uozumi, Y.; Kimura, T. *Synlett* **2002**, 2045..(c) Palladium complexes immobilized on dendrimer modified silica and their application in the Heck reaction have also been reported: Alper, H.; Prabhat, A.; Bourque, S. C.; Jefferson, G. R.; Manzer, L. E. *Can. J. Chem.* **2000**, *78*, 920.

(6) **General Experimental Procedure**: All reactions are carried out under an atmosphere of argon using Schlenk-techniques. Aminomethyl-resin beads (**1**) are carefully degassed by swelling the beads in dry toluene and removing the solvent in vacuo (repeated 1×) (This procedure is necessary to avoid P(V) formation during the preparation of **3** due to trapped oxygen molecules in untreated **1**. Meanwhile, a second Schlenk flask is charged with paraformaldehyde (4 equiv), dry MeOH and diphenylphosphine (4 equiv). This reaction mixture is heated to 60 °C until the white suspension forms a colorless solution. After removal of MeOH in vacuo the remaining viscous oil is diluted in dry toluene. This solution is added to the beads swollen in dry toluene. The reaction mixture is heated to 105 °C overnight. In the cooler regions of the flask the water–toluene azeotrope separates indicating the reaction progress. After cooling to r.t. the beads are collected by filtration under argon. The beads are washed extensively with dry toluene (4×), CH$_2$Cl$_2$/THF (1/1) (2×) and CH$_2$Cl$_2$ (2×). The beads are dried in vacuo until the weight remains constant. We have successfully applied this procedure for the preparation of **3** using several types of polystyrene resins (varying in grain size, degree of cross-linking, and loading), Tentagel-resin, and macroporous beads.

(7) **Experimental Procedure for Ligand Metathesis**:
All reactions are carried out under an argon atmosphere using Schlenk-techniques. To polystyrene beads **3** (3 g, 2.31 mmol), swollen in 120 mL degassed CHCl$_3$, is added 1.1 equiv (COD)PdCl$_2$. The reaction mixture is heated at 60 °C for 26 h. After cooling to r.t. the beads are collected by filtration under argon. The beads are washed extensively with degassed CHCl$_3$ (4 × 40 mL), EtOH (1 × 40 mL) and dry CH$_2$Cl$_2$ (3 × 40 mL). The beads are dried in vacuo until the weight remains constant. Elemental analysis: 0.81% N, 3.22% P, 5.72% Pd (elemental analyses have been carried out by Mikroanalytisches Laboratorium H. Kolbe, Mülheim/Ruhr).

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(10) **Representative Experimental Procedure: Synthesis of Diphenylacetylene (7a):**
In a light protected Schlenk-flask polystyrene-supported Pd-catalyst **4** (44.2 mg, 0.024 mmol Pd) was allowed to swell 5 min under argon atmosphere in degassed 1,4-dioxane: piperidine (2:1) (15 mL). Iodobenzene (**5a**) (1.5 mmol, 306.3 mg), phenylacetylene (**6a**) (2.1 mmol, 214.8 mg) and copper(I)iodide (0.03 mmol, 5.8 mg) were added to the catalyst. The mixture was slowly stirred under argon at 60 °C for 2 h. The Pd-beads were separated from the mixture by filtration and washed with CH$_2$Cl$_2$ (4 × 20 mL). The solution was washed with a sat. solution of ammonium chloride (1 × 30 mL) (this extractive step removes Cu-impurities by formation of the water soluble Cu-tetraamine complex) and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 15 mL). The combined organic layers were dried over Na$_2$SO$_4$ and the solvent removed in vacuo. Purification by flash chromatography (SiO$_2$, pentane) provided 265.2 mg **7a** (99%, colorless crystals).

(11) Polymeric bound Pd catalyst **4** can be stored for several months without any significant loss of activity (Schlenk flask, argon, 4 °C).