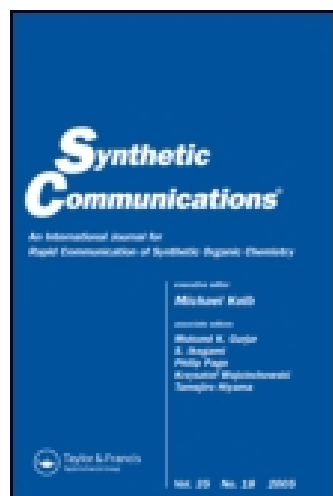


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HETEROGENEOUS CATALYZED REDUCTION OF POLYMER-BOUND NITROARENES

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ABSTRACT

Deposition of palladium as a catalyst on polymer beads, such as Merrifield resin or TentaGel, allows the reduction of polymer-bound 4-nitro benzoate to the corresponding anilines with dilute hydrazine hydrate solution in DMF at room temperature.

Reactions of polymer-bound organic substrates have become very important in the last decade.^{1,2} Solid phase protocols allow combinatorial preparation of compounds,³ automation of synthesis or simplicity of handling and work-up during synthesis. The number of reactions for which solid phase procedures exist has increased markedly in recent years.⁴ However, for reduction steps, such as the reduction of nitro compounds, very few procedures are available.⁵ Homogeneous reduction

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reagents⁶ such as SnCl_2 ^{7–12} or $\text{CrCl}_2/\text{Mn}/\text{TMSCl}$,^{13,14} which have been employed in solid phase synthesis, have significant disadvantages: The procedures are not general and success strongly varies with substrate structure. Stoichiometric amounts of toxic metals are necessary, and the procedures are not easily applied in automated synthesis. The classical and well-established methods for reduction in homogeneous solution with heterogeneous transition metal catalysts and a hydrogen source,^{15,16} if used in solid phase synthesis, lead to an unfavorable situation of two heterogeneous reaction components. However, the problem might be resolved if the catalytic site and polymer-bound substrate are brought in close contact.¹⁷ In this paper we present our results in adapting a well known catalyzed heterogeneous reduction reaction to a solid phase protocol.

To make heterogeneous catalyzed reactions on polymer-bound substrates possible, we deposit palladium as the active metal catalyst directly on the polymer bead used for solid phase synthesis.¹⁸ Standard Merrifield resin (**1a**) was loaded with 4-nitro benzoic acid (**2**) using Cs_2CO_3 and potassium iodide in DMF (see Scheme 1 for conditions).¹⁹ The hydrogenation catalyst was then precipitated on the polymer by heating the loaded bead with palladium acetate in DMF for 1 h to 80°C. The beads turned dark black indicating the precipitation of finely divided palladium. From high resolution inductively coupled plasma mass spectrometry (HR-ICP-MS) a palladium content of 9500 $\mu\text{g Pd}$ per gram of resin was determined. Analysis of DMF solutions in which the palladium loaded beads were stored for 24 h gave a very low palladium content of 2–3 $\mu\text{g Pd/ml}$, which indicates that the palladium is strongly bound to the surface and not rapidly released from the bead into solution. In order to gain information about the structure of the precipitated palladium, REM images of the beads with and without palladium were recorded (see Figure 1). Even at high magnification no significant differences of the surface structure were observed, from which we conclude a fine distribution of the palladium over the whole surface.²⁰

The resin, now loaded with nitroarene substrate and palladium metal, was treated with 20% (v/v) hydrazine hydrate solution in DMF at room temperature. Instantaneous gas evolution indicates a spontaneous reaction. To ensure complete conversion the beads were left in the solution overnight and washed with DMF several times. A positive bromo phenol blue assay²¹ confirmed the presence of free amino groups on the bead. 4-Amino benzoic acid methyl ester (**8a**) was cleaved from the resin with sodium methoxide in methanol and isolated in 60% yield. The presence of palladium as a catalyst is essential for the reaction. Treatment of nitroarene-loaded Merrifield resin with hydrazine solution without palladium deposition gave no conversion of starting material. Palladium precipitation and the reduction step can be combined into one

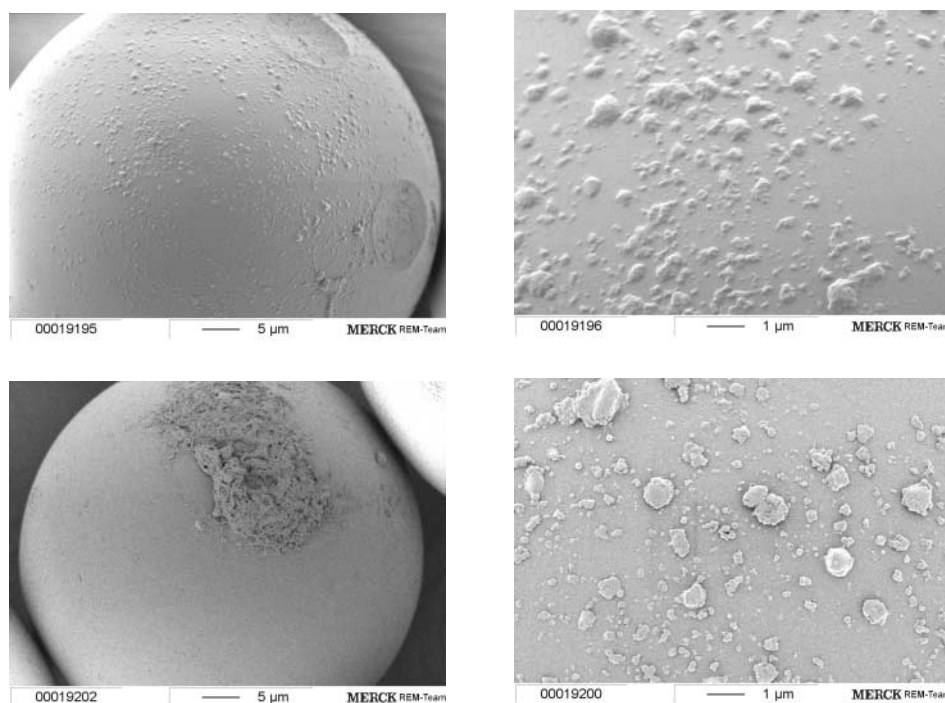
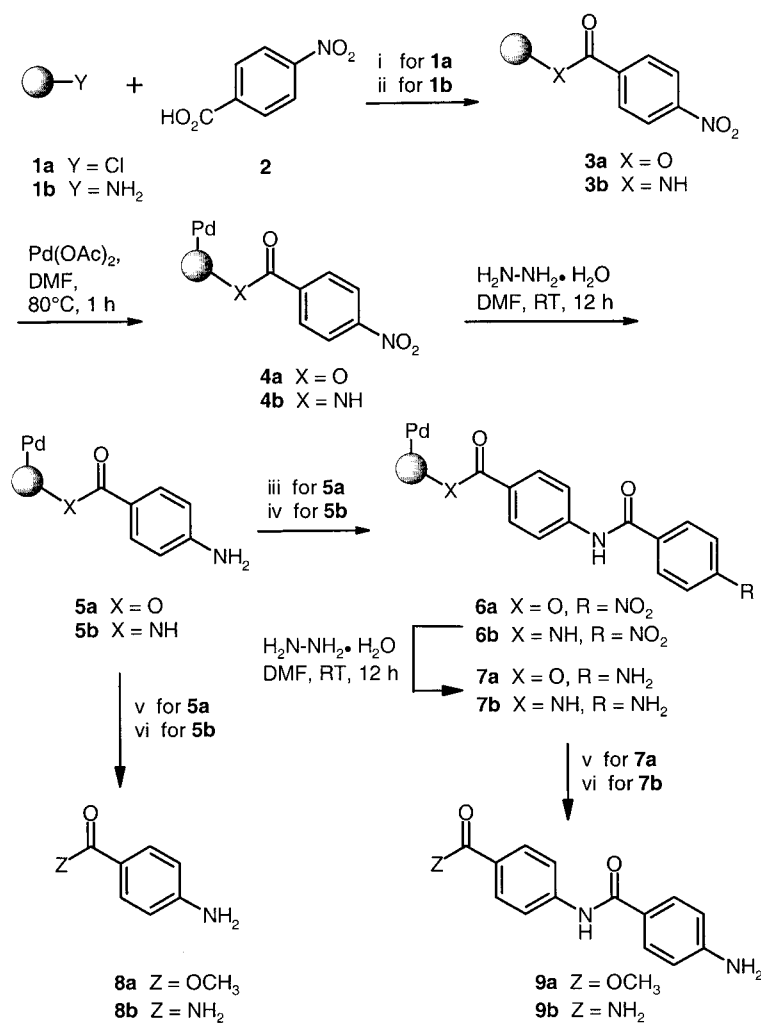


Figure 1. REM images of Merrifield resins with (lower pictures) and without (upper pictures) precipitated palladium at low (left pictures) and high (right pictures) magnification.

step, whereby palladium acetate and hydrazine hydrate solution are added simultaneously. This allows a direct conversion of compound **3a** and **5a**.²² Treatment of **5a** with excess 4-nitro benzoyl chloride gave **6a**, which was treated with hydrazine hydrate solution for 12 h. Cleavage of the product from the resin gave **9a**, although in low yield of 28%. This shows that in principle the deposited catalyst can be reused for subsequent catalytic steps performed on the bead, but at the present stage loss of catalyst activity is significant.

To prove the compatibility of the method with more advanced materials and techniques of solid phase synthesis, the procedure was performed on TentaGel S RAM (**1b**),²³ a TentaGel with rink amide linker group. Using standard conditions, 4-nitro benzoic acid (**2**) was coupled to the solid support. The loading capacity of the bead was verified by cleavage of the bound substrate with TFA as amide, whereby 99% of the compound

was reisolated in analytical pure form. Palladium was precipitated on the bead as described above, and treatment of the loaded bead with 20% (v/v) hydrazine hydrate solution in DMF for 12 h at room temperature, washing with DMF and cleavage of the product with TFA gave **8b**²⁴ in 94% isolated



Scheme 1. Reagents and conditions: (i) Cs₂CO₃, KI, DMF, 72 h, 80°C; (ii) DIC, HOBT, Et₃N, DMF, RT, 12 h; (iii) 4-Nitrobenzoyl chloride, Et₃N, DMF; (iv) **2**, DIC, HOBT, Et₃N, DMF, RT, 12 h; (v) NaOMe, MeOH, RT, 12 h; (vi) TFA/CH₂Cl₂ (5:95); RT, 1 h.

yield. A second coupling/reduction cycle of **5b** via **6b** and **7b** gave **9b** after cleavage from the resin. However, again the isolated yield of 30% is not satisfactory and the stability of the catalyst on the resin must be increased before extended reaction sequences can be performed.

The scope of this method is limited by the chemoselectivity to other reduceable functional groups in the substrate, as in comparable reduction reactions. In addition the reaction of 1-chloro-5-nitro benzoic acid was not successful, most likely due to the chemical reactivity of the chloroarene bond in the presence of palladium. However, the method facilitates the use of the large number of known and available aromatic and heteroaromatic nitro compounds in library synthesis on solid support.

In conclusion we have shown that polymer-bound 4-nitro benzoate can be reduced to the corresponding aniline in 94% overall yield at room temperature by treatment with hydrazine solution if palladium as a catalyst is precipitated on the TentaGel bead.²⁵ These experiments are first and simple examples of catalytic beads that are loaded, in addition to the immobilized substrate, with tools for catalytic and selective chemical transformations on their surface.

EXPERIMENTAL

Typical procedure for the reduction-coupling cycle on TentaGel S RAM: A suspension of 500 mg resin-bound nitrobenzamide **3b** in 5 ml of DMF with 5 mg palladium (II) acetate was heated for 1 h to 80°C. The resin was filtered off, washed with DMF and dichloromethane and dried in vacuo. The palladium-loaded resin **4b** was stirred in 5 ml of 20% (v/v) hydrazine hydrate/DMF solution for 12 h at room temperature, the resin was filtered off, washed with DMF, methanol and dichloromethane and dried in vacuo. The reaction product was cleaved by treatment with TFA (5% in dichloromethane solution) to give **8b** in 94% isolated yield or coupled again with **2** to yield **9b** after reduction and TFA cleavage from the resin.

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19. The loading capacity of the resin was determined by cleaving the ester from the loaded bead with sodium methoxide in methanol at room temperature. from the yield of 4-nitro benzoic acid methyl ester (**8a**) a capacity of 0.6 mmol/g of polymer bead was calculated.
20. Deposition of palladium onto the resin at room temperature is possible by addition of hydrazine hydrate to the palladium salt solution. properties of the beads are similar as described above. Experiments to deposit palladium from palladium salt solution using ultrasound were not successful.

21. A sample of the beads was suspended in dichloromethane and a drop of a 1% solution of bromo phenol blue in dimethylacetamide was added. A deep blue staining of the beads indicates the presence of free amino groups.
22. The palladium content of the beads and the solution was determined as described before, which confirmed that under the reaction conditions of the reduction the palladium is still present on the bead and is not released into solution.
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