Microwave-Assisted Suzuki–Miyaura Reactions with an Insoluble Pyridine-Aldoxime Pd-Catalyst

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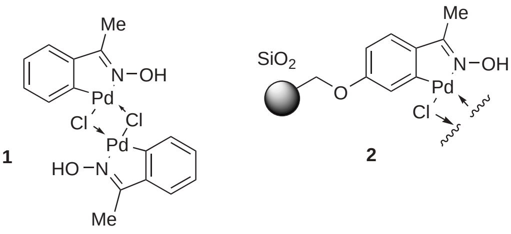
Abstract: The preparation of a solid Pd(II)-precatalyst and its use in microwave-assisted Suzuki–Miyaura reactions in water is described. The precatalyst is obtained by treatment of 4-pyridine-aldoxime with Na_2PdCl_4 and is insoluble in organic solvents as well as in water. Its robustness under microwave conditions and its insolubility allows simple reuse in 'teabags'.

Key words: Suzuki–Miyaura reactions, precatalyst, pyridine-aldoxime Pd-catalyst

Palladium-mediated cross-coupling reactions play an important role in organic synthesis. A group of new ligands for palladium derives from aromatic oximes which have been known since the early 1970s.[1] Only in the last years they were discovered to be efficient precatalysts for C-C cross-coupling reactions.[2] Often, these compounds are dimeric chloro-bridged *ortho*-palladated complexes such as the acetophenone oxime-based palladacycle **1** (Figure 1) utilized by Nájera et al., which is a versatile precatalyst for several carbon-carbon coupling reactions.[2] Reusable heterogeneous precatalysts[3] for Suzuki–Miyaura reactions were prepared by covalently anchoring complex **1** via the arylether linkage to modified silica gel yielding precatalyst **2**.[4]



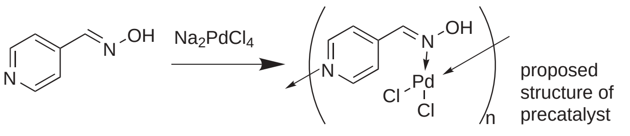
1

2

Figure 1

An alternative to anchoring homogeneous precatalysts to a solid phase are catalysts, which are heterogeneous themselves. Insolubility in common reaction media allows simple removal of the catalyst at the end of the reaction. At the same time, this approach leaves out additional reaction steps for immobilization. Here, we report on a modified aromatic oxime ligand for coordination to palladium(II), which is insoluble in organic solvents and can be utilized like an immobilized catalyst. In addition, we show that this heterogeneous precatalyst can repeatedly be employed under microwave irradiation conditions.[5]

4-Pyridine-aldoxime served as a ligand, which upon treatment with sodium tetrachloropalladate, led to a precipitate and was insoluble in most organic solvents (in DMF and DMSO little solubility was encountered) as well as in water (Scheme 1). Filtration and washing with methanol and water and drying yielded a material which in contrast to oxime palladacycles **1** did not show a Pd-C σ-bond in the ^1H NMR spectrum (all four hydrogen atoms of the pyridine ring can be detected in deuterated DMF). This fact found additional support by the ^{13}C NMR spectrum and by combustion analyses of **3**. So far, the precise structure could not be elucidated but we propose a quasi polymeric complex in which the oxime and the pyridine nitrogen atoms are involved in complexation.



3

Scheme 1

The Suzuki–Miyaura cross-coupling reaction between phenyl boronic acid (1.5 equiv) and *p*-bromo-acetophenone (1.0 equiv) (according to Scheme 2 but under thermal conditions) served as a model reaction for evaluating the activity of this new material. The reaction proceeded in toluene at 110 °C (2 equiv K_2CO_3, 1 mol% **3**) under air in less than 50 minutes, a clear indication of the high activity of complex **3**. The product was isolated in 95% yield. The particles **3** could be recollected and repeatedly used for two additional coupling reactions, each time full transformation was achieved within 1 hour.[6] We observed that, after an induction phase, the material turns dark and the catalytic process is initiated. At this stage, the nature of the active palladium species is not clear. In this context it needs to be mentioned that de Vries and co-workers recently conducted a careful study on ligand-free palladium-catalyst in Heck reactions.[7] They found that a low concentration of Pd(0) is a key issue for high activity. Higher concentrations than 0.1 mol% led to the formation of substantial amounts of inactive Pd black. Importantly, the authors note that palladacycles behave similarly and it

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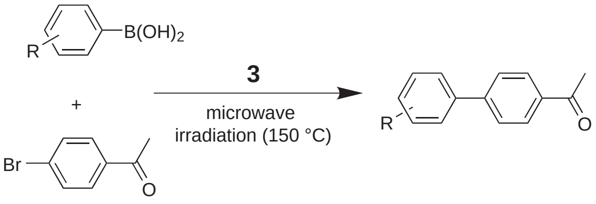
was concluded that they also merely serve as source for ligand-free palladium. This interpretation cannot be excluded in the current case.

In the next phase we tested the utility of this insoluble complex under microwave irradiation conditions (Table 1).[8,9] Water turned out to be superior to toluene, an observation which was supported when other substituted aryl-boronic acids were coupled under the same conditions (reaction time: 300 sec, see Table 2).



Scheme 2[a]

Table 1 Utility of the Insoluble Complex under Microwave Irradiation Conditions with Various Reaction Times

R = H	60 s	120 s	180 s	240 s
Toluene	90%	79%	87%	98%
Water	94%	94%	98%	98%

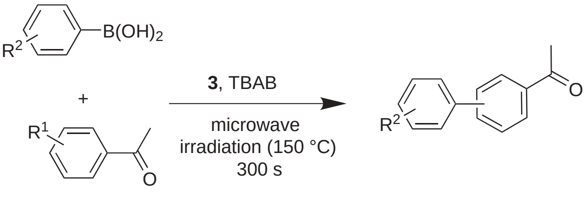
Table 2 Reaction Time: 300 s[a]

R =	H	4-Me	3-CF$_3$	4-SMe	4-Cl
Toluene	70%	79%	62%	39%	69%
Water	99%	85%	89%	59%	76%

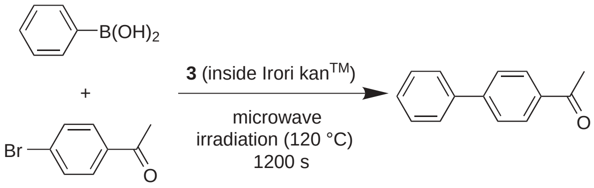
[a] Conditions: Aryl bromide (1 mmol), boronic acid (1.5 mmol), K_2CO_3 (2 mmol) and **3** (1 mol%); the degree of transformation was analyzed by LC/MS.

A comparison study between the soluble Nájera precatalyst **1** and the new insoluble precatalysts **3** was conducted using differently well suited reaction partners (Scheme 3, Table 3). This investigation revealed that **1** is less active compared to **3** in Suzuki–Miyaura reactions when moderately active pairs of coupling partners are chosen while reactive and unreactive partners behave similarly in the presence of both precatalysts.

Then, we tested the stability and recyclability of the new catalyst. For this purpose we enclosed **3** (1 mol%) inside an Irori kan^{TM} and carried out the coupling of phenyl boronic acid with 4-bromo acetophenone under microwave irradiating conditions at 120 °C (restrictions are due to the thermal stability of the Irori kan^{TM}, Scheme 4, Figure 2). The reaction was terminated by removal of the can which was washed prior to use. Even the 14th run with the reused can give 93% of conversion within 20 minutes. These results indicate sufficient stability and activity (>1200 TON for all 14 runs) of the catalyst under these microwave conditions.



Scheme 3



Scheme 4

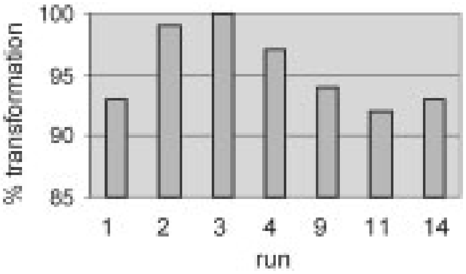


Figure 2

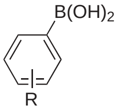
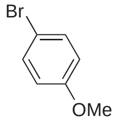
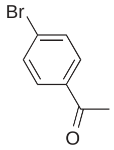
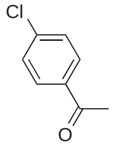
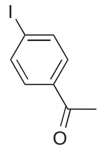
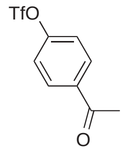
Under these optimized conditions (water, microwave irradiation 120 °C, TBAB, 1200 s) a small compound library of biaryls was prepared. While the chosen arylboronic acids showed structural and electronic diversity, the second reaction partner was mainly based on acetophenone with differing halogen substituents and the triflate group, respectively. Gratifyingly, also 4-chloro acetophenone served as coupling partner in the Suzuki–Miyaura reaction.[10]

Table 3 Comparison Study between Soluble Nájera Precatalyst **1** and the New Insoluble Precatalyst **3**

R^1 R^2	4-Br 4-OH	2-Cl H	4-I 4-Cl	4-Cl 4-Cl	4-I H	4-Cl H
Precatalyst **1**	N.r.[a]	N.r.	56%	50%	92%	86%
Precatalyst **3**	N.r.	N.r.	81%	87%	92%	84%

[a] N.r. = no reaction; aryl halogenide (1 mmol), boronic acid (1.5 mmol), K_2CO_3 (2 mmol), tetrabutylammonium bromide (TBAB; 1 mmol), **3** (1 mol%) in 3.5 mL H_2O; the degree of transformation was analyzed by GC/MS.

Table 4 Small Compound Library of Biaryls[a,b]

					
H	88%	100%	84%	92%	91%[c]
2-CF$_3$	84%	96%	75%	N.d.[d]	82%[c]
4-Cl	75%	83%	87%	81%	77%[c]
4-SMe	87%	90%	N.d.[d]	86%	82%[c]
3-CF$_3$	95%	95%	79%	96%	59%[c]
4-OMe	83%	98%	87%	91%	56%[c]
4-NH$_2$	48%	65%	0%	98%	N.d.[d]

[a] Conditions: **3** (1 mol%), boronic acid (1.5 mmol), halide (1 mmol), K_2CO_3 (2 mmol), TBAB (1.0 mmol) in H_2O (3.5 mL).

[b] Except for column 2 (isolated yields) yields were determined by GC; thus loss of material during workup and isolation was determined to be less than 5%.

[c] Reduced and non-optimized yields due to partial degradation of triflate

[d] Not done.

Finally, we checked whether the catalyst is actually required under microwave heating. Indeed, Leadbeater and coworkers recently noted that Suzuki-type reactions can be achieved in the absence of any transition metal precatalyst with microwave irradiation.[11] In this work it was noted that the presence of tetrabutylammonium bromide in water is essential for successful coupling. In the present case, the Suzuki–Miyaura reaction did not take place under comparable conditions as described above [4-bromoacetophenone (1 mmol), phenylboronic acid (1.5 mmol), TBAB (1 mmol) in 3.5 mL H_2O, at 150 °C in the absence of **3**].

In summary, we developed a new insoluble Pd(II)-precatalyst, which is conveniently prepared by mixing of readily available 4-pyridinealdoxime with Pd(II) salts.[12] The catalyst which is heterogeneous in nature is insoluble in water as well organic solvents. Loaded inside an Irori kan™ (‘teabag’) it repeatedly promotes the Suzuki–Miyaura reaction under microwave irradiating conditions. The concept of insoluble precatalysts without use of an additional solid phase can be broadened towards more active and broadly usable precatalysts, which are currently investigated in our laboratories.

Preparation of Precatalyst 3. A solution of 4-pyridine-aldoxime (122 mg, 1 mmol) in MeOH (1 mL) was added dropwise to the stirred solution of sodium tetrachloropalladate(II) (294 mg, 1 mmol) in MeOH (2 mL). Gentle stirring was continued overnight, the precipitate was filtered, washed with MeOH and H_2O, and dried in vacuum over P_2O_5. Precatalyst **3** was obtained as orange brownish powder (288 mg, 0.96 mmol; 96%). The ^{1}H NMR spectrum reveals the presence of isomers in a ratio of about 2:1. Similar findings have been reported for other palladium catalysts with ligands containing N-donors.[13]

3: IR: ν = 1611 cm^{-1}. ^{1}H NMR (400 MHz, DMF-d_7): δ = 7.76 and 7.81 (2 d, 2 H_{Py}), 8.29 and 8.34 (2 s, CH=N), 8.70–9.00 (m, 2 H_{Py}), 12.53 and 12.57 (2 s, 1 H, O*H*). ^{13}C NMR (100 MHz, DMF-d_7): δ = 154.06, 146.3, 144.5, 122.6. Anal. Calcd for $C_6H_6Cl_2N_2OPd$: C, 24.07; H, 2.02; N, 9.35. Found: C, 24.08; H, 2.41; N, 9.17.

Selected spectroscopic data for the palladium-free ligand: IR: ν = 1603 cm^{-1}. ^{13}C NMR (100 MHz, DMF-d_7): δ = 150.9, 147.4, 141.4, 121.4.

General Procedure for the Suzuki–Miyaura Reaction under Microwave Irradiating Conditions (Table 4). Precatalyst **3** (3 mg; 1 mol%) was inclosed inside an Irori kan™, and was added to a reaction mixture consisting of boronic acid (1.5 mmol), aryl halide (1.0 mmol), tetrabutylammonium bromide (1 mmol) and K_2CO_3 (2 mmol) in H_2O (3.5 mL). The suspension was subjected to microwave irradiating conditions (Emrys™ Optimizer from Personal Chemistry). The reaction was heated for 1200 sec at 120 °C and then cooled. The Irori kan™ was removed and washed with EtOAc (2 mL). The outcome of the reaction was monitored by GC- or HLPC analysis. The reaction phase was extracted with EtOAc (2 × 10 mL). The combined washing and extracts were concentrated under reduced pressure and the crude product was purified by column chromatography (silica gel; solvent mixtures consisted of EtOAc–cyclohexane).

When the heterogeneous precatalyst **3** was directly added to the reaction mixture (not inside the Irori kan™) the reactions were irradiated at 150 °C for 300 s. It could be recollected by filtration.

After filtration the filtrate was checked for catalytic activity by adding an additional portion of phenylboronic acid and 4-bromoacetophenone. Under identically conducted reaction conditions, no transformation to the biaryl derivatives was observed. However, when the Irori kans™ were utilized as filtration aid, we found some activity in the solution for the first three or four runs when the teabag had been removed which can be rationalized by the fact that the finest catalyst particles had left the can into solution. After the 4th run, however, no catalytic activity was released into solution any more while the catalyst inside the Irori kan™ still exerted catalytic activity (see Scheme 4).

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