DOI: 10.1002/adsc.200800575

Supported Palladium Catalysts for Suzuki Reactions: Structure-Property Relationships, Optimized Reaction Protocol and Control of Palladium Leaching

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Received: September 17, 2008; Revised: November 10, 2008; Published online: December 10, 2008

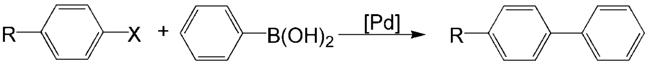
Abstract: Palladium on metal oxides and on activated carbon with particular properties (high palladium dispersion, low degree of reduction, water content) are shown to be highly active (tunrover number, TON=20,000; turnover frequency, TOF=16,600), selective and robust catalysts for Suzuki cross-couplings of aryl bromides and activated aryl chlorides. Catalysts and reaction protocol offer combined advantages of high catalytic efficiency under ambient conditions (air and moisture), easy separation and reuse and quantitative recovery of palladium. The palladium concentration in solution during the reaction correlates clearly with the progress of the reaction and indicates that dissolved molecular palladium is in fact the catalytically active species. Dissolved palladium is redeposited onto the support at the end of the reaction. Additional minimization of the palladium content in solution (down to 0.1 ppm) could be achieved by simple procedures which meet the requirements of pharmaceutical industry.

Keywords: heterogeneous catalysis; leaching; palladium; Suzuki–Miyaura reaction

Introduction

Palladium-catalyzed C−C bond formation reactions are a versatile tool in organic synthesis. Among these the Suzuki coupling reaction (Scheme 1) is of particular importance. It involves the reaction of aryl halides with arylboronic acids to yield unsymmetrical biaryls with high selectivity. The reaction is unique, requiring mild reaction conditions and showing a high degree of tolerance for a variety of functional groups.[1]

For this reaction, a multitude of highly efficient catalytic systems based on soluble and immobilized palladium (pre)catalysts have been developed but complications for commercial operations exist due to high metal costs and stringent requirements for the removal of residual metal from product and waste materials. Palladium-catalyzed reactions are often used by pharmaceutical industries in the synthesis of medicinal compounds and must meet government requirements of ≤5 ppm residual metal in the product.[2] These costs and purification pressures have spurred significant research in two distinct areas: (i) development of highly active homogeneous catalysts that are active at ppm metal concentrations and (ii) immobilization of palladium so that it can be recovered and reused.[3]



R = H, CH_3, OCH_3, CN, $COCH_3$, OH
X = Br, Cl

Scheme 1. Suzuki couplings of aryl halides and phenylboronic acid.

In the past few years, a number of attempts and strategies have been used to get a commercially viable, highly active, recoverable, and reusable palladium catalyst for Suzuki reactions.[4] A substantial number of reports claiming "true" heterogeneous catalysis by supported palladium (i.e., on the noble metal surface) in Suzuki reactions have been published.[5] Other authors found that Suzuki reactions are catalyzed by palladium dissolved in solution (leaching).[6] On the other hand, the mechanism of another heterogeneously catalyzed carbon-carbon coupling reaction, the Heck reaction, is clearly better understood nowadays due to a remarkable number of detailed mechanistic investigations and literature reports.[3,7] A variety of different experimental approaches demonstrates rather clearly that – for Heck reactions – supported palladium catalysts serve as a reservoir for active palladium species leached into solution.[8,9] In other words, palladium is dissolved from the solid catalyst surface under the reaction conditions forming the active molecular palladium species. Palladium is partially or completely re-deposited onto the support at the end of the reaction when the aryl halide is consumed. The palladium dissolution-redeposition processes as well as catalytic activity are strongly influenced by the reaction conditions.[9] A better understanding of analogous phenomena in heterogeneously catalyzed Suzuki reactions is of particular relevance for the aforementioned separation of catalyst and palladium from reaction mixture and products, for possible reuse of the catalysts as well as for optimization of catalyst performance and reaction protocol. In the last few years, there has been an increasing interest to access the true catalytic species in Suzuki reactions catalyzed by supported catalysts. Commonly used tests for this purpose are based on hot filtration, comparing final yields after recycling and the use of solid poisons.[3,6a] These techniques provide interesting information about the nature of palladium species under specific conditions but can also lead to wrong conclusions. Therefore, in the Suzuki investigations presented here, we focus on a straightforward and direct method already successfully applied for Heck reactions, which is based on the determination of palladium leaching during the reaction.

The enormous knowledge about (heterogeneously catalyzed) Heck reactions can also help with the optimization of supported palladium catalysts and reaction conditions for Suzuki couplings. The best catalyst performances for Heck reactions were achieved for palladium supported on carbon and on metal oxides, when palladium was highly dispersed on the support surface as palladium(II) (oxide or hydroxide) and when the catalysts contained rather high water contents.[9c] The influence of the support has been found to be of minor or no importance for catalytic performance.[10] Corresponding reports do not exist for Suzuki couplings until now. Moreover, palladium on carbon has been most extensively researched for Suzuki reactions so far.[11] Very few investigations on metal oxide-supported catalysts and no comparative studies concerning determination of palladium leaching have been reported as yet for Suzuki reactions. For palladium supported on alumina-based oxides, Gniewek et al. proposed a truly heterogeneous mechanism, whereby palladium nanoparticle surfaces represent the active species. This conclusion is based on the lack of change in the sizes of palladium particles on the surface after completion of the reaction.[12]

In the present paper, we report that carefully selected procedures for catalyst preparation (analogous to Heck catalysis)[9b] and optimized reaction conditions strongly influence palladium leaching during (and deposition at the end of) Suzuki reactions. Skilled preparation of the catalyst and careful adjustment of the reaction conditions allowed the development of highly active and robust heterogeneous catalysts (Pd/metal oxide, Pd/C), converting aryl bromides and (activated) aryl chlorides in Suzuki reactions in high yields (100%) and short reaction times. Conclusions drawn should support synthetic and industrial organic chemists in choosing simple, optimized solid catalysts and reaction conditions for this type of reaction. In addition, highly efficient quantitative separation of palladium from the reaction mixture will be addressed.

Results and Discussions

Pd/C *vs.* Pd/MO$_x$ Precatalysts in Suzuki Reactions

As proposed in the introduction, we first applied a preparation procedure for supported palladium catalysts that had been originally optimized for Heck reactions. In order to achieve high dispersion of palladium(II) species, the catalyst has been prepared by controlled precipitation of palladium(II) hydroxide.[13] Drying and reduction at elevated temperatures must be avoided. An optimized reaction procedure of an earlier report on Suzuki couplings was applied for the following catalytic experiments.[14] The chosen, commercially available Pd/activated carbon (Pd/C) catalyst shows high activity and selectivity in the Suzuki reaction of phenylboronic acid with various aryl bromides in NMP/water (NMP = 1-methyl-2-pyrrolidone) mixture as solvent (Table 1). All aryl bromides, activated or deactivated, investigated under the reaction conditions presented here can be quantitatively coupled with phenylboronic acid within two hours using extremely low palladium equivalents (0.005–0.01

Table 1. Heterogeneous Suzuki coupling of aryl bromides with phenylboronic acid.[a]

Entry	R in Scheme 1	Catalyst [mol%]	Yield[b] [%]	TON	TOF [h^{-1}]
1	CN	0.01	100	10,000	6666
2	H	0.005	100	20,000	10000
3	OH	0.01	100	10,000	5000
4	OCH$_3$	0.005	100	20,000	10,000

[a] *Reaction conditions:* aryl bromide (10 mmol), phenylboronic acid (11 mmol), NMP (10 mL), H_2O (4 mL), Na_2CO_3 (12 mmol), 5% Pd/C (E 105 CA/W), $T = 120\,°C$, 1.5–2 h.

[b] GC yield of cross-coupled product taking diethylene glycol dibutyl ether as internal standard.

Table 2. Conversion and yield of thermally pretreated catalysts in Suzuki coupling of 4-bromoanisole and phenylboronic acid.[a]

Entry	Pretreatment conditions	*t* [h]	Yield[b] [%]	TON	TOF [h^{-1}]
1	pretreated under H_2 at 300 °C	2	67	335	168
2	pretreated under H_2 at 300 °C	4	68	340	85
3	pretreated under N_2 at 500 °C	2	33	165	83
4	pretreated under N_2 at 500 °C	4	34	170	43

[a] *Reaction conditions:* 4-bromoanisole (10 mmol), phenylboronic acid (11 mmol), NMP (10 mL), H_2O (4 mL), $T=120$ °C, sodium carbonate, 0.2 mol% Pd (E 105 CA/W 5% Pd/C), thermally pretreated at 300 °C or 500 °C).

[b] GC yield.

mol%). This catalyst belongs to the very best heterogeneous catalysts for Suzuki couplings showing turnover numbers (TON) of up to 20,000. A selectivity of 100% for the Suzuki cross-coupled product is found nearly without exception (Table 1; note: aryl chlorides show no conversion under these conditions).

In contrast, thermally treated catalysts show only small catalytic activity in the Suzuki reaction of 4-bromoanisole and phenylboronic acid (Table 2). TON and TOF (TOF = turnover frequency) decreased by at least two orders of magnitude compared to the values of the non-reduced catalyst (compare with Table 1). These catalysts contain mainly or exclusively palladium in its reduced state Pd(0) clearly indicating that catalysts with higher oxidation states (i.e., Pd^{2+}) are better precursors for high activity under these reaction conditions.

Palladium supported on Al_2O_3, TiO_2 or CeO_2 were prepared according to the same procedure in order to evaluate the influence of the support with identical or similar nature of surface palladium. Pd/zeolite (NaY) catalyst preparation is also reported in the literature.[15] All catalysts are active and show high conversions of 4-bromoanisole under the aforementioned conditions (NMP/water, 120 °C, 2 h). In particular, palladium on alumina and titania show the same high activity as Pd/C. After 2 h, nearly complete conversion is reached and the selectivity is 100%. Pd/CeO_2 and palladium incorporated into NaY require somewhat longer reaction times to reach high yields.

In all cases, the selectivity is 100% (Table 3). Thus, there is only a limited influence of the support as compared to the preparation procedure and the resulting properties of Pd catalysts (oxidation state, dispersion, water content). It can be concluded that it is the nature of the supported palladium (and carefully selected reaction protocols) and not the nature of the support that are decisive for efficient Suzuki couplings.

Table 3. Heterogenous Suzuki coupling of 4-bromoanisole and phenylboronic acid by different Pd/MO_x catalysts.[a]

Entry	Catalyst	t [h]	Yield[b] [%]	TON	TOF [h^{-1}]
1	Pd/Al_2O_3	2	96	19,200	9600
2	Pd/TiO_2	2	97	19,400	9700
3	Pd/CeO_2	4	82	16,400	4100
4	Pd/NaY	4	82	16,400	4100

[a] *Reaction conditions:* NMP (10 mL), water (4 mL), $T=120$ °C, sodium carbonate, 0.005 mol% Pd.

[b] GC yield.

Table 4. Heterogeneous Suzuki coupling of 4′-chloroacetophenone with phenylboronic acid.[a]

Entry	Catalyst	Additive	Yield (4-acetylbiphenyl)[b] [%]
1	Pd/Al_2O_3	none	30
2	Pd/Al_2O_3	TBAB	88
3	Pd/C	TBAB	100

[a] 4′-Chloroacetophenone (10 mmol), phenylboronic acid (11 mmol), sodium hydroxide (12 mmol), TBAB (where mentioned: 3 mmol), NMP (10 mL), water (3 mL), 0.1 mol% [Pd], $T=120$ °C.

[b] GC yield.

It is well known that the Suzuki coupling of aryl chlorides is clearly more demanding. Applying the same optimized catalyst, it would be necessary to change the reaction parameters. Most important factors are the addition of tetra-*n*-butylammonium bromide (TBAB) and changing the base from Na_2CO_3 to NaOH. These small changes result in remarkably high conversion of 4′-chloroacetophenone (Table 4) with Pd/C as well as with Pd/Al_2O_3 (4′-chloroacetophenone has been chosen as aryl chloride substrate because it can more easily be activated as compared to aryl chlorides with electron-donating substituents and thus is better comparable to bromoanisole).

Conversion as a function of reaction time is illustrated in Figure 1 for the reaction of 4′-chloroacetophenone with phenylboronic acid and shows this dramatic influence clearly. The strong increase of activity in the presence of TBAB may be due to stabilization of dissolved palladium species (against agglomeration) in the reaction mixture. Corresponding explanations of these effects are given in the literature.[16]

Palladium Leaching during the Reaction

Some of the (probably) wrong conclusions in the literature claiming a "truly" heterogeneous character of

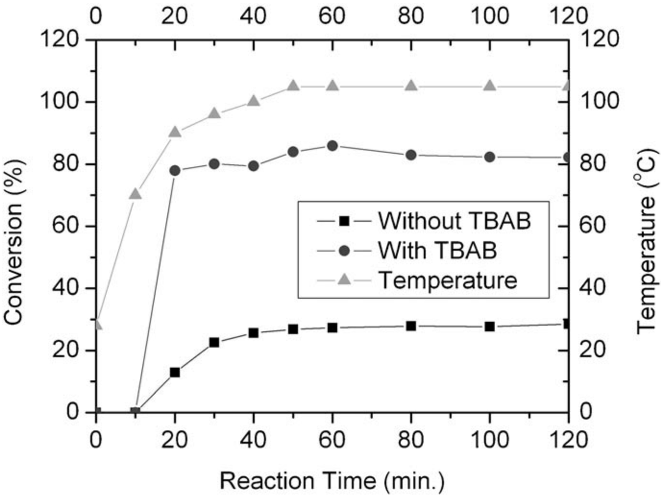


Figure 1. The effect of TBAB as an additive for the Suzuki coupling of 4′-chloroacetophenone with phenylboronic acid. *Reaction conditions:* 4′-chloroacetophenone (1 equiv.), phenylboronic acid (1.2 equiv.), NaOH (1.5 equiv.), 0.1% Pd/Al_2O_3, NMP/water, 120 °C.

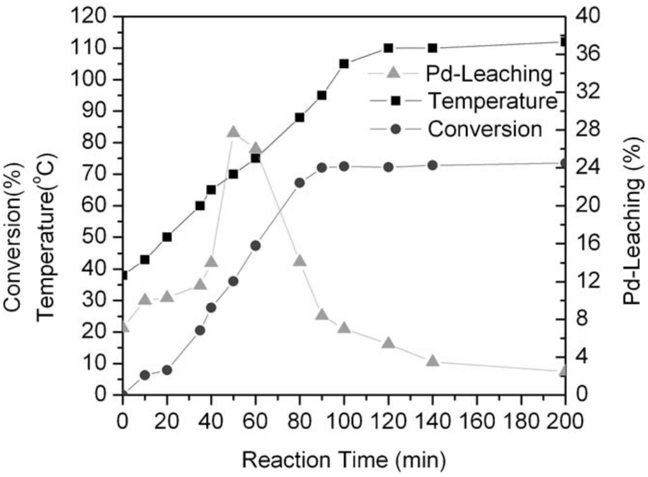


Figure 2. Time-dependent correlation of palladium leaching with the progress of the reaction. *Reaction conditions:* 1 equiv. 4-bromoanisole (116 mmol), 1.1 equiv. Na_2CO_3 (128 mmol), 1.1 equiv. $PhB(OH)_2$ (128 mmol), NMP:water 250:100 mL, 0.1 mol% Pd/Al_2O_3,maximum temperature of oil bath: 120 °C.

Suzuki reactions are due to the fact that measurable amounts of palladium are often observed in solution only during the reaction. Because of re-deposition, the palladium concentration in the solution is very small or undetectable at the end of the reaction. In addition, extremely low amounts of palladium in the ppm or sub-ppm range are highly active but possibly not detectable by the analytical tools chosen for mechanistic studies. Controlled re-deposition of dissolved palladium would ideally lead to supported palladium as highly dispersed in the successive runs as in the first run. Under such conditions, palladium particles before and after catalysis are expected to be very similar and not proof for a heterogeneous mechanism as concluded in the literature.[12] The nature and role of the various palladium species in C−C coupling reactions with heterogeneous catalysts and the value and limitations of corresponding test experiments have been conclusively discussed and illustrated in reviews on heterogeneous Heck catalysis.[7d,e]

In order to address the homogeneous or heterogenous nature of the reaction, the palladium concentration in solution was determined as a function of reaction time and temperature. Since no influence of the support on activity and selectivity was found, we selected self-prepared Pd/Al_2O_3 for the coupling of 4-bromoanisole with phenylboronic acid as a model reaction. The experiment was carried out in a 500-mL flask under the optimized reaction conditions (NMP/water, Na_2CO_3, 120 °C), and the progress of the reaction (conversion, yield) was monitored by simultaneous determination of the concentration of palladium in solution. The samples were taken in short intervals with careful observation of any rise in temperature. A part of the reaction mixture was hot filtered directly into a small round-botton flask to determine palladium content of the solution (flame AAS), while the remaining part was extracted with dichloromethane to get the conversion of 4-bromoanisole (GC). The results (Figure 2) show a direct correlation between the reaction progress and the amount of dissolved palladium species in solution. A sharp increase in the conversion of 4-bromoanisole is related to the maximum palladium amount leached into the solution. It is interesting to note that this happens at temperatures lower than 100 °C. This is in contrast to analogous experiments carried out for Heck reactions, where – for the same substrates – palladium leaching and conversion started only at temperatures of or above 140 °C. Obviously, the mechanism of palladium leaching is different in both reactions. However, what is valid for Suzuki as well as for Heck reactions is the general mechanism that palladium is dissolved from the support into solution at the beginning and during the reaction and re-deposited after the reactants have been consumed. What also becomes clear from comparable experiments (not shown) is the strong influence of the reaction parameters (type of reaction, substrate, temperature, additive, solvent and base) on the leaching.

Recycling of Pd/Al_2O_3

Recycling of the catalyst can be of considerable importance for practical applications. Again the Pd/Al_2O_3-catalyzed Suzuki reaction of 4-bromoanisole was investigated in more detail regarding catalyst recycling (Table 5). In particular, application of

Table 5. Recycling of Pd/Al_2O_3 in the Suzuki coupling of 4-bromoanisole and phenylboronic acid.[a]

Cycle	Conversion [%]	Yield [%]
Fresh Catalyst	99	99
1st recycle	76	76
2nd recycle	71	71
3rd recycle	66	66
4th recycle	69	69

[a] *Reaction conditions:* NMP (10 mL), H_2O (4 mL), T = 120 °C, 4 h, sodium carbonate, 0.2 mol% [Pd], 0.1 mmol of I_2.

0.1 mmol of I_2 as an agent for partial re-oxidation of reduced palladium as reported by De Vries et al. led to very satisfying results.[17]

A slight gradual decrease in activity was observed during five successful runs and the fifth run corresponded to 69% conversion with 100% selectivity to cross-couplled product (Table 5). Probable reasons for the loss of activity are only partial re-oxidation of Pd(0) to Pd(II) by I_2 and somewhat lower palladium dispersion after re-deposition.

Minimizing Palladium Content in Solution at the End of the Reaction – Palladium Re-Deposition and Separation

Since the use of supported palladium catalysts is also motivated by the ease of catalyst separation, palladium leaching can be an important limitation. The following experiments demonstrate, however, that the catalytic systems reported here allow efficient re-deposition of palladium onto the support. Trace analysis (ICP-OES) of the reaction mixture after two hours (the usual reaction time) shows only 0.5 ppm palladium (based on the mass of palladium in solution *versus* the total mass of the reaction mixture) in the solution. The palladium contents in the product are expected to be even smaller. In order to reduce the palladium content further, a series of experiments have been performed. The Suzuki coupling of 4-bromoanisole and phenylboronic acid after the typical reaction time (2 h) was followed by additional treatments considered to be favorable for re-deposition of the noble metal onto the support. This included heating of the reaction mixture to higher temperatures and/or the addition of reducing agents (sodium formate).[18]

After additional treatment for 2 h at 120 °C, the palladium content in solution was reduced from 0.5 ppm to 0.44 ppm. After additional treatment of the reaction mixture at 140 °C for 2 h palladium content is reduced to 0.32 ppm. The palladium content in solution was further remarkably diminished by the addition of sodium formate. The lowest Pd residue in solution (0.12 ppm) was obtained by adding 6 mmol of sodium formate and heating for 2 h at 140 °C (Figure 3). In principle all results (palladium contents < 1 ppm) meet the expectations of the pharmaceutical industry.

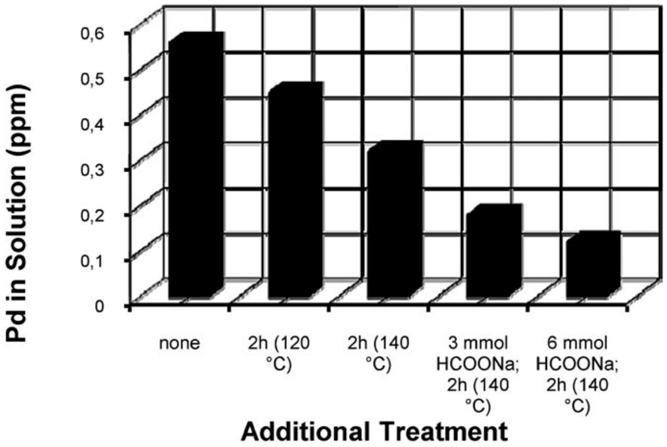


Figure 3. The influence of prolonged reaction time and/or addition of sodium formate as reducing agent on palladium content in solution in the Suzuki coupling of 4-bromoanisole and phenylboronic acid. *Reaction conditions:* 10 mL of NMP, 3 mL of water, sodium carbonate, 120 °C, 2 h, 0.02 mol% Pd/C.

Conclusions

Skilled preparation led to supported palladium catalysts (Pd/C, Pd/MOx, Pd/zeolite) combining extremely high activity, short reaction times and 100% selectivity in Suzuki reactions of aryl bromides and activated aryl chlorides with the advantages of easy and complete Pd separation and recovery. The reaction system is easy to handle and stable against moisture and air. Neither inert atmosphere nor ligands are necessary. The choice of base and solvent is crucial for the efficiency of the reaction. The influence of the support (activated carbon, metal oxides, zeolite) on the activity and selectivity in the Suzuki reactions studied can be neglected, whereas the preparation procedure and the resulting properties of Pd catalysts (oxidation state, dispersion, water content) are significant.

The Pd concentration in solution during the reaction correlates clearly with the progress of the reaction (conversion) and indicates that dissolved molecular palladium represents the catalytically active species. Dissolved Pd is deposited onto the support at the end of the reaction.

The Pd concentration in solution at the end of the reaction can be minimized to 0.12 ppm by easily applicable procedures (heating, addition of reducing agents after the reaction has finished). The catalysts can be recycled and efficiently reused several times by the addition of an oxidizing agent (iodine).

Experimental Section

The catalytic reactions were carried out in pressure tubes in air or under argon. All reactants and solvents were obtained from Aldrich, Fluka or Merck (grade p.a.) and were used as received without further purification or drying. The qualitative and quantitative analysis of the reactants and products was performed by gas-liquid chromatography (GLC) or GC-MS. Products were identified by comparison with authentic samples. Conversion and selectivity are represented by product distribution (=relative area of GLC signals) and GLC yields (=relative area of GLC signals referenced to an internal standard calibrated to the corresponding pure compound, $\Delta_{rel} < \pm 5\%$).

The gas-liquid chromatograph is an HP 6890 series equipped with an FID detector and an HP-1 column (cross-linked methylsiloxane, 30 m × 0.25 mm × 0.25 μm film thickness). GC-MS analyses were performed on an HP 5890 instrument with an HP 5970 mass detector and an HP-1 column.

The palladium content in solution was determined by ICP-OES on a Perkin–Elmer Optima 3300 DV spectrograph and ICP-MS by a VG Elemental Plasmaquad 2+ spectrograph.

Catalyst Preparation

The catalysts were obtained by wet impregnation.[13] All catalysts were prepared using H_2PdCl_4 at a constant Pd loading of 5 wt%. The support material (specific surface area by BET: Al_2O_3: 195 $m^2 g^{-1}$; TiO_2: 49 $m^2 g^{-1}$; CeO_2: 58 $m^2 g^{-1}$) was first suspended in distilled water. Then an aqueous solution of the Pd compound was added. After impregnation and heating to 80 °C the suspension was adjusted to pH 10 by adding sodium hydroxide. After further agitation the slurry was filtered and washed with distilled water. The catalysts were used after drying at room temperature for 24 h. Pd/C is commercially available and was used as delivered (Evonik-Degussa AG).

Procedures for Catalytic Tests

Bromoarene (5 mmol; usually 4-bromoanisole, 0.935 g), phenylboronic acid (5.5 mmol; 0.670 g), base (6 mmol; usually sodium carbonate 0.636 g), diethylene glycol-*n*-dibutyl ether (0.250 g, as an internal standard for GC analysis) and 0.005–0.2 mol% of Pd as a heterogeneous catalyst were introduced into a pressure tube. NMP and water were added, the mixture was optionally purged with argon and placed in a preheated oil bath. The reaction was performed with vigorous stirring at the specified temperature for 1–2 h.

For the GLC analyses a sample (1 mL) taken from the reaction mixture before filtration was quenched with water (2 mL) in a test tube. This mixture was extracted with dichloromethane (2 mL), the organic layer was filtered and dried over $MgSO_4$. The resulting dry organic layer was analyzed by GLC or GC-MS.

Determination of Palladium Content in Solution

For the determination of the Pd content in solution, 5 mL of the reaction mixture were filtered hot (0.45 μm syringe filter, polypropylene membrane) into a 10-mL round-bottom flask. After careful evaporation of the liquids, using direct heating on an aluminum block, the sample was treated with sulfuric acid and nitric acid, diluted, filtered and analyzed by atomic spectroscopy (inductively coupled plasma-optical emission spectroscopy, ICP-OES, or inductively coupled plasma-mass spectroscopy, ICP-MS). For better accuracy, multiple analyses were carried out for each sample.

Kinetic Experiment

4-Bromoanisole (116 mmol), Na_2CO_3 (128 mmol, 1.1 equiv.), $PhB(OH)_2$ (128 mmol, 1.1 equiv.), and 0.1 mol% of the Pd catalyst (1% Pd/Al_2O_3) were weighed into a 500-mL flask. NMP (250 mL) and of water (100 mL) were added and the flask was placed in a preheated oil bath at 80 °C. The reaction mixture (7 mL) was withdrawn at intervals with careful observation of reaction time and temperature. The sample solution (5 mL) was directly syringe filtered into a 10-mL round-bottom flask for palladium analysis and 2 mL were extracted with dichloromethane to get yields from GLC. The temperature of the oil bath was gradually increased to 120 °C and the sample taking continued for about 3 h.

Recycling Procedure

Reactions were performed as mentioned above. After cooling, the mixture was washed three times with 10 mL of CH_2Cl_2 and centrifuged (6000 rpm, Biofuge primo R, Heraeus) for 10 min. Starting with the second cycle 0.1 mmol I_2 was added.

Acknowledgements

The authors thank the Bayerische Forschungsstiftung and the Fonds der Chemischen Industrie (Germany) for financial support. S.S.S. acknowledges the Bayerische Forschungsstiftung for a grant. Dr. J. Krauter and Dr. P. Panster (Degussa AG/Evonic Industries) are acknowledged for technical support and helpful discussions.

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