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Palladium leaching dependent on reaction parameters in Suzuki–Miyaura coupling reactions catalyzed by palladium supported on alumina under mild reaction conditions

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ABSTRACT

Suzuki couplings of aryl bromides as well as activated aryl chlorides can be efficiently performed by palladium supported on alumina under mild reaction conditions ($T = 65\,^{\circ}C$). The catalyst prepared by controlled precipitation of palladium hydroxide shows a high activity and represents a perfect and robust alternative to other complex and expensive preparation procedures. Palladium leaching in the Suzuki couplings by supported palladium catalysts has been investigated in detail for the first time for such mild reaction conditions. Catalytic activity is due to palladium species dissolved from the solid particles. The active palladium species in solution are re-deposited onto the support with the completion of the reaction. Catalytic activity correlates with the amount of palladium dissolved. Palladium leaching is a prerequisite for highly efficient catalysis in particular for more demanding substrates. Palladium leaching depends on a variety of parameters (temperature, solvent, base, substrates, and additives). Transmission electron microscopic investigations show that – depending on the parameters – the efficient palladium re-deposition process can leave the catalyst with an unchanged dispersion and particle size distribution after the reaction.

1. Introduction

Carbon–carbon bond forming reaction of aryl halides with arylboronic acids (Suzuki–Miyaura reaction, Scheme 1) has become an efficient and clean strategy for the preparation of unsymmetrical biphenyls, which are important building blocks for pharmaceutical and agricultural industries [1–4]. Motivated mainly by an easy separation and reuse of the supported palladium catalysts, a number of novel heterogeneous catalysts have been developed for these reactions. Several materials have been applied as supports for the noble metal. Most commonly carbon [5–13] but also other materials [14–25] have been exploited as supports to prepare highly active heterogeneous catalysts for Suzuki coupling reactions. It has been demonstrated however that specific properties, in particular of the supported palladium species (high dispersion, low reduction degree), are more relevant for high activity of the catalyst than the nature of the support itself. Thus, catalysts prepared by controlled precipitation of palladium(II) hydroxide show highest activity (when not thermally pre-treated or reduced) [26–29].

Recently, alumina–zirconia-mixed oxide-based palladium catalysts (Pd(II)/Al_2O_3–ZrO_2) have been reported [30] as highly active for Suzuki reactions of aryl bromides under mild reaction conditions (60 °C). A completely heterogeneous mechanism has been proposed based on the TEM investigations of the used catalysts. One subject of our present report is the generalization and transfer of these results to the successful activation of aryl chlorides under such mild reaction temperatures. This improves the potential of the simple Pd/Al_2O_3 catalysts without requiring any complex preparation procedures. At the same time, our basic aim is to investigate the nature of the active palladium species and the mechanism of potential Pd leaching under such mild conditions.

Palladium leaching has become an issue of increasing interest in the field of catalysis, in particular with carbon–carbon coupling reactions. The main interest in noble metal leaching arises from very practical aspects namely the separation of the catalyst from the reaction mixture being related to the metal content at the end of the reaction (loss of expensive catalyst, contamination of products). There are however other aspects, why leaching investigations are important. Thus, a knowledge-based optimization of catalyst and reaction parameters is not in fact efficiently possible without knowing whether molecular dissolved noble metal species or a solid surface of a noble metal particle is the true catalytically active species. Especially for Heck reactions, it has been demonstrated and proven that the activity of supported catalysts is due to dissolved molecular palladium species that re-deposit onto the

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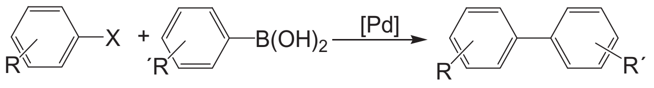


Scheme 1. Suzuki couplings of aryl halides and phenylboronic acids.

support after the consumption of the reacting substrates [27,31,32]. There have also been several efforts in recent years to show that Suzuki reactions using heterogeneous catalysts are catalyzed by soluble palladium species [24,33–37]. On the other hand, a considerable number of reports have been published recently claiming "true" heterogeneous reactions catalyzed by the solid surface of palladium particles [8,14,18,38–43]. The conclusion of "heterogeneity" is mainly drawn on the basis of few common tests, i.e. hot filtration at the end of the reaction, final yields of successive runs and also sometimes the initial and final particle size distribution of the catalyst used in the reaction. These tests, when carefully combined with additional mechanistic investigations, can give useful information on the actual mechanism [32]. On the other hand, opposite conclusions could also be drawn as already explained on the basis of different examples from published literature reports [37]. The correlation of palladium content in solution with the reaction yield as function of reaction time is a direct and unambiguous method to establish the nature of catalysis and has been successfully applied to Heck reactions [44]. The method demonstrates a time-dependent Pd dissolution–re-deposition processes with Heck reactions. Recently, we reported the first analogous investigation and thus the evidence of palladium leaching during Suzuki reactions at temperatures of 120 °C [45]. Although the phenomenon of leaching during the reaction is the same, it has been hypothesized that the mechanism of Pd leaching is different for Heck and Suzuki reactions. The present reaction system allows us to investigate for the first time the nature of the active palladium species (Pd leaching) under mild conditions, i.e. at 65 °C. In addition, transmission electron microscopy (TEM) measurements show that palladium particle size distributions are not significantly changed compared before and after the Suzuki reactions (due to efficient re-deposition) though substantial amounts of Pd (>50 mol%) had been temporarily dissolved during the reaction.

Very recently, a detailed mechanistic study for the Suzuki coupling reaction of aryl iodides has been published [46] in which authors concluded a surface-catalyzed reaction under the chosen, very specific reaction conditions. The present investigations demonstrate clearly that the Pd leaching as well as the catalyst activity are largely dependent on the selected reaction parameters, and the effects are even more pronounced for the more demanding substrates (deactivated aryl bromides or chlorides).

2. Experimental

2.1. Materials and methods

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 referred to an internal standard calibrated to the corresponding pure compound, $\Delta_{rel} < \pm 5\%$). The palladium content in solution was determined by flame atomic absorption spectroscopy (FAAS). The transition electron microscopy (TEM) measurements were performed on a JEOL 100CX microscope that operates with an accelerating energy of 100 kV. The used catalysts were washed with dichloromethane and water before TEM investigations. Boron NMR spectra of the reaction mixture were recorded on a JEOL JMX-GX 400 spectrometer operating at 400 MHz without using any external standard or deuterated solvent.

2.2. Catalyst preparation

The catalysts were prepared by controlled precipitation deposition of palladium(II) hydroxide onto the aluminum oxide support [47]. They were prepared using $PdCl_2$ dissolved in diluted (5%) HCl. A final Pd loading of 1–5 wt.% on metal oxides has been adjusted. The support material was first suspended in distilled water. Then, an aqueous solution of the Pd compound was added. The suspension has then been adjusted to a pH = 10 with the help of autotitrator (736 GP Titrino, Metrohm) using 10% sodium hydroxide solution under continuous stirring. After further agitation, the slurry was filtered, washed with distilled water and dried at room temperature for 24 h.

Modification of the catalyst surface was carried out by calcinations and subsequent reduction under hydrogen flow. Air-dried Pd/Al_2O_3 (prepared as mentioned earlier) was calcined in a Naberthem (30–3000 °C) oven with air flow using a heating rate of 2 K/min from r.t. to 500 °C. The temperature was maintained at 500 °C for 2 h after which it was cooled down to r.t. "calcined" catalyst was collected as brown colored powder. Pd(0)/Al_2O_3 ("reduced" catalyst) was obtained by treating the "calcined" catalyst with pure hydrogen with a flow rate of 70 mL/min in a U-reactor. The temperature was maintained at 350 °C for 2 h after which the reactor was cooled down to r.t. under a flow of argon.

2.3. Procedures for catalytic tests

Bromoarene (2.9 mmol, 1 eq.), phenylboronic acid (3.2 mmol, 1.1 eq.), sodium carbonate (3.2 mmol, 1.1 eq.), diethyleneglycol-*n*-dibutylether (250 mg, as an internal standard for GC analysis) and 0.1 mol% of Pd as supported catalyst were introduced into a pressure tube. In a typical Suzuki reaction of aryl chloride, 4′-chloroacetophenone (2.9 mmol, 1 eq.), phenylboronic acid (3.2 mmol, 1.1 eq.), and sodium hydroxide (4.4 mmol, 1.5 eq. instead of sodium carbonate) were used along with 1 mmol TBAB (tetra-*n*-butyl ammonium bromide) as additive. NMP (1-methyl-2-pyrrolidone) and water were added; the mixture was optionally purged with argon and placed in a pre-heated oil bath. The reaction was performed with vigorous stirring at the specific temperature for 2–4 h. Argon atmosphere was obligatory to get good yields for the Suzuki coupling reactions of 4′-chloroacetophenone, whereas it was not a requirement for the activation of aryl bromides.

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.

2.4. Kinetic experiments (correlation of Pd content in solution and reaction yield, *f(t)*)

Bromobenzene (116 mmol, 1 eq.), Na_2CO_3 (128 mmol, 1.1 eq.), $PhB(OH)_2$ (128 mmol, 1.1 eq.), and 0.1 mol% of the Pd catalyst (Pd/Al_2O_3) were weighed and added to a 500-mL flask. Then, 250 mL of NMP and 100 mL of water were added. The flask was placed in a pre-heated oil bath at 65 °C after deaerating the reaction mixture by purging argon for 5 min. Seven milliliters of the reaction mixture was withdrawn at intervals with careful observation of reaction time and temperature. Five milliliters of the sample solution was directly syringe filtered into a 10-mL round bottom flask for palladium analysis, whereas 2 mL was extracted by dichloromethane to get yields via GLC. The reaction was monitored for 5 h, and samples were collected after short intervals of time.

2.5. Determination of palladium content in solution (influence of reaction parameter)

For the determination of the Pd content in solution, the mixture containing the solid catalyst was allowed to stir at 65 °C for 1 h after which 5 mL of the reaction mixture were hot filtered (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 flame AAS. For better accuracy, multiple analyses were carried out for each sample. In addition, the filtered solution has been analyzed by UV–vis spectroscopy that indicated molecular palladium halide complexes and no colloid or palladium black.

2.6. ^{11}BNMR experiment

Bromobenzene (14.5 mmol, 1 eq.), phenylboronic acid (16 mmol, 1.1 eq.), and sodium carbonate (16 mmol, 1.1 eq.) were weighed and added to a 100-mL three-neck flask. NMP/water mixture (52.5 mL, with the ratio 5:2) was added. After purging with argon, the reaction mixture was stirred for half an hour at room temperature to make it as homogenous as possible. First sample for boron NMR was drawn from the reaction mixture at this stage followed by the addition of the catalyst (Pd/Al_2O_3, 0.1 mol%). The flask was quickly brought into the pre-heated oil bath (65 °C). After stirring the reaction mixture for 5 min, the second sample for NMR was withdrawn. Subsequent samples were taken in the same way and were measured simultaneously after being syringe filtered directly into the NMR tube.

3. Results and discussion

3.1. Activity of Pd/Al_2O_3 in Suzuki reactions of aryl bromides and aryl chlorides at 65 °C

3.1.1. Activation of aryl bromides

First, the activity of the air-dried Pd/Al_2O_3 catalyst was tested at 65 °C under argon applying the reaction conditions that were already optimized for Suzuki reaction at 120 °C [28]. The results were encouraging, showing 68% yield in Suzuki coupling reaction of 4-bromoanisole within 5 h with very low amount (0.1%) of the catalyst.

Further, a couple of reactions were performed in order to see the influence of the catalyst modification (Fig. 1). The calcination procedure leads to removal of water from the catalyst, and additional reduction with hydrogen results in an increasing content of palladium(0) particles. As depicted in Fig. 1, the thermally treated catalysts show lower activity and loss of selectivity, especially for the reduced catalyst. These experiments indicate that the catalysts with higher Pd oxidation state (i.e. Pd^{2+}) are better precursors to achieve high activity under these reaction conditions as demonstrated already for Heck reactions [26] as well as for Suzuki reactions as higher temperatures [28]. As will be demonstrated later (Section 3.3), this difference in catalytic activity is consistent with the considerably reduced Pd leaching from thermally treated catalysts when compared to the non-treated ones.

The influence of various reaction parameters on Suzuki couplings catalyzed by Pd/Al_2O_3 are shown in Table 1. These experiments have been performed in order to optimize the reaction at temperatures of 65 °C and to allow a later correlation of reaction parameter and Pd leaching into solution (see Sections 3.2 and 3.3). The suitable NMP (1-methyl 2-pyrrolidone) to water ratio was found to be 5:2 (Table 1). A variety of aryl bromides could be coupled efficiently within short reaction times. Chloro- and fluoro-substituents remain unaffected under these reaction conditions (entries 7 and 9). Hence, the reaction conditions can selectively be applied for the attack at carbon–bromine bond. For a comparison, the Suzuki coupling reaction of 4-bromoanisole was also carried out under argon or at high temperature (Table 2). The results indicate that inert atmosphere is not necessary for the reactions, in contrast, the reaction proceeds with somewhat higher reaction rate in the presence of air (entry 4). As expected, shorter

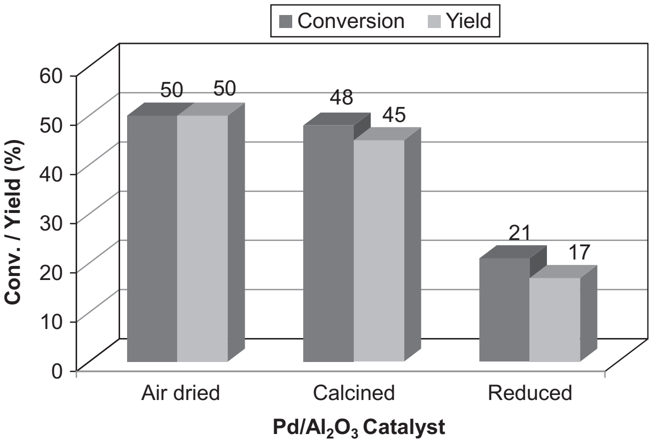


Fig. 1. Effect of catalyst pre-treatment on the reaction yield. Reaction conditions: 4-bromoanisole (2.9 mmol), sodium carbonate (3.2 mmol), phenylboronic acid (3.2 mmol), 0.06 mol% of Pd (0.6% Pd/Al_2O_3), NMP:water 5:2 mL, 65 °C, 4 h, air. Air-dried = catalyst used after drying at RT for 24 h. Calcined = catalyst calcined at 500 °C for 2 h. Reduced = catalyst reduced under pure H_2, at 350 °C for 2 h.

Table 1
Suzuki coupling of aryl bromides with phenylboronic acid.

Entry	R in Scheme 2	Water (mL)	Time (h)	Conversion[a]	Yield[b] (%)
1	$COCH_3$	0	3	22	21
2	$COCH_3$	1	3	72	72
3	$COCH_3$	2	3	100	100
4	H	2	4	95	95
5	OCH_3	2	5	68	68
6	NO_2	2	3	100	100
7	Cl	2	3	95	95
8	CHO	2	3	100	100
9	F	2	3	96	96

Reaction conditions: Aryl bromide (2.9 mmol), sodium carbonate (3.2 mmol), phenylboronic acid (3.2 mmol), 0.1 mol% of Pd (1% Pd/Al_2O_3), NMP = 5 mL, 65 °C, argon.

[a] Conversion of aryl bromide.

[b] GC-yield of cross-coupled product.

Table 2
Effect of temperature and atmosphere on Suzuki coupling of 4-bromoanisole with phenylboronic acid.

Entry	Temperature (°C)	Atmosphere	Time (h)	Yield[a] (%)
1	120	Argon	4	80
2	120	Air	2	72
3	65	Argon	5	68
4	65	Air	4	80

Reaction conditions: 4-bromoanisole (2.9 mmol), sodium carbonate (3.2 mmol), phenylboronic acid (3.2 mmol), 0.1 mol% of Pd (1% Pd/Al_2O_3), NMP:water 5:2 mL.

[a] GC-yield of cross-coupled product.

reaction times are required at higher temperatures. The acceleration of the reaction is however clearly less pronounced than expected from kinetic arguments. This indicates again that several reaction parameters have a significant influence on the reaction rate. A lower catalyst concentration was also tried but the product (4-methoxybiphenyl) yield dropped from 68% (0.1 mol% Pd) to 58% with 0.06 mol% Pd and below 10% with 0.01 mol% Pd.

3.1.2. Activation of aryl chlorides

As shown in Table 1 (entry 7), aryl chlorides were not converted under the reaction conditions given. The activation of aryl chlorides is also not addressed in the reports published about the Suzuki coupling reactions, where alumina or alumina–zirconia mixed oxides were used as the catalyst supports under such mild conditions [30,48]. It is well known that the activation of aryl chlorides is clearly more demanding than that of aryl bromides or iodides. Hence, we investigated the Suzuki reaction of 4′-chloroacetophenone and phenylboronic acid at the same temperature of 65 °C with varying reaction conditions (base, TBAB). Among various bases screened, sodium hydroxide was found to be the best in the presence of TBAB as additive (Fig. 2). Thus, it is possible to activate aryl chlorides bearing electron-withdrawing substituents under these mild conditions using only 0.1 mol% of palladium.

The role of TBAB has been well documented in literature and is believed to stabilize the palladium nanoparticles as well as anionic Pd bromo complexes in the reaction mixture [49–51]. As will be demonstrated via Pd-leaching investigations (Section 3.3), TBAB also helps to stabilize the dissolved Pd species in solution, thus allowing maximum contact between the active Pd species and the substrates. Such stabilization is necessary for the activation of aryl chlorides.

Lowering the palladium concentration to 0.05 mol% resulted in slight decrease in yield. Further decrease in palladium content reduces conversion as well as selectivity to the desired cross-coupled product substantially.

Thermally treated Pd/Al_2O_3 catalysts resulted in lower catalyst activity. Thus, compared to air-dried catalysts (conversion 78% in 4 h with 100% selectivity), pre-treated catalysts (calcination at 500 °C for 2 h; reduction with H_2 at 350 °C for 2 h) reduce the conversion by a factor of 10 and selectivity to the cross-coupling product to less than 15%. These results demonstrate a significant influence of chosen reaction parameters in Suzuki–Miyaura coupling reactions. The outcome of experiments performed on the catalyst activity can be used to establish a more generalized approach toward selection of the heterogeneous Pd catalysts for these reactions.

3.2. Palladium leaching during the reaction

It has been demonstrated for Heck reactions [26,27,52,53] and very recently for Suzuki reactions [45] at higher temperature (120 °C) that palladium is dissolved from the support during the reaction and (for the most part) re-deposited onto the support at the end of the reaction, when substrates have been consumed. Fig. 3 represents the results of analogous experiments for Suzuki coupling reactions catalyzed by Pd on alumina under mild conditions (65 °C). Bromobenzene was chosen as substrate for these experiments due to several experimental reasons. Loss in information on selectivity (no substituent at the aromatic ring) is not problematic because 100% selectivity to the cross-coupling products has been found without exception in all coupling reactions with Pd/Al_2O_3 as depicted by the results in Table 1.

In Fig. 3, the palladium concentration in solution as well as the conversion of bromobenzene is presented as a function of reaction time and temperature. The palladium content in solution rises with time and increasing temperature. After about 75 min, more than 50% of the palladium supported on alumina is leached into the solution. Thereafter, a continuous decrease in the amount of dissolved palladium is observed down to 10% of the total palladium amount at 320 min. At this stage, the palladium content remaining in the solution is about 5 ppm. Parallel to Pd leaching, the conversion of bromobenzene rises smoothly from the beginning till 180 min after which it stays at its highest value (96%). The Pd content in solution starts to decrease when high percentage of bromobenzene has been converted (>60%). This correlation of conversion and Pd content in solution is analogous to former investigations at higher temperatures (Heck, Suzuki; see above). However, the

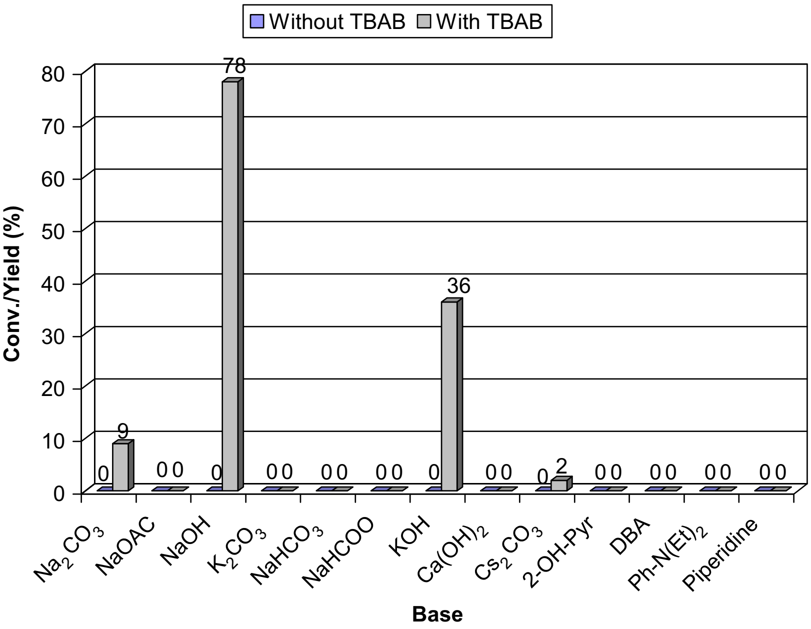


Fig. 2. Activation of 4′-chloroacetophenone for Suzuki coupling reaction at 65 °C. Reaction conditions: 4′-chloroacetophenone (2.9 mmol, 1 eq.), base (4.5 mmol, 1.55 eq.), phenylboronic acid (3.2 mmol, 1.1 eq.), TBAB (1 mmol), 0.1 mol% of Pd (1% Pd/Al_2O_3), NMP:water 5:2, argon, 4 h, 65 °C. 2-OH-Pyr = 2-hydroxypyridine, DBA = dibenzyl amine.

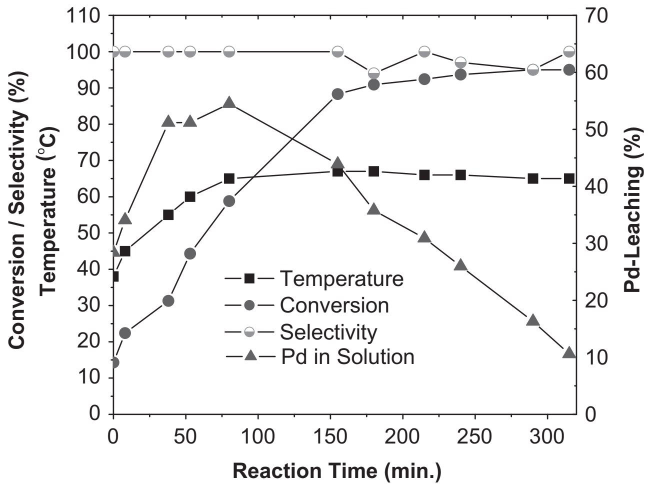


Fig. 3. Correlation of Pd leaching and conversion in the Suzuki reaction of bromobenzene with phenylboronic acid. Reaction conditions: Bromobenzene (116 mmol, 1 eq.), Na_2CO_3 (128 mmol, 1.1 eq.), $PhB(OH)_2$ (128 mmol, 1.1 eq.), NMP:water 250:100 mL, 0.1 mol% of Pd (1% Pd/Al_2O_3), $T = 65$ °C.

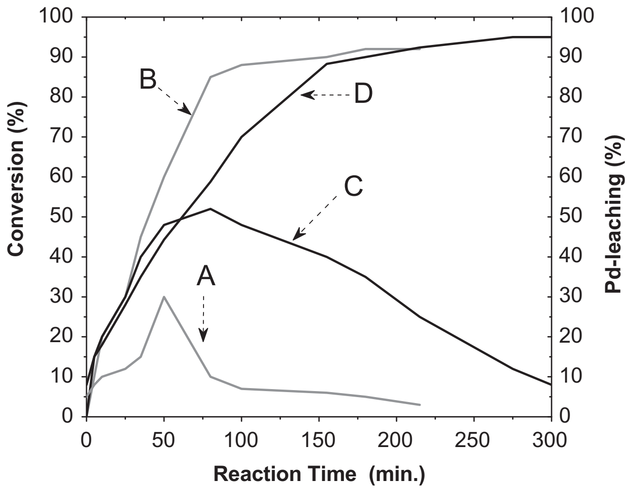


Fig. 4. A presentation of Pd leaching and conversion in Suzuki coupling reactions at different temperature ranges; (A) Pd leaching at 120 °C (see Ref. [45]), (B) conversion of aryl bromide at 120 °C, (C) Pd leaching at 65 °C, (D) conversion of aryl bromide at 65 °C (Fig. 3).

effects are less pronounced at the lower temperature (65 °C), i.e. the corresponding leaching curve is clearly broader in this case (as depicted in Fig. 4).

When comparing Pd leaching at different temperatures, e.g. at 65 °C (present investigations) and 120 °C [45], it must be taken into account that the stability of the palladium complexes in solution is higher at lower temperatures. Higher temperatures lead to quicker re-deposition of the metal and, vice versa, the leaching at these higher temperatures is more difficult. This effect has been applied for more efficient catalyst separation to avoid product contaminations being important e.g. in the pharmaceutical industry [54].

In particular, the phenomenon is different when compared to Heck reactions. The palladium leaching (and substrate conversion) starts even at room temperature in the present Suzuki experiment and does not require a higher minimum temperature ("induction period") as observed in investigations regarding Heck reactions, starting only at higher temperatures [26,55]. Accordingly, an oxidative addition of the aryl halide to a surface palladium atom cannot be the driving force of palladium dissolution in this case as often hypothesized for Heck reactions at 140 °C [56].

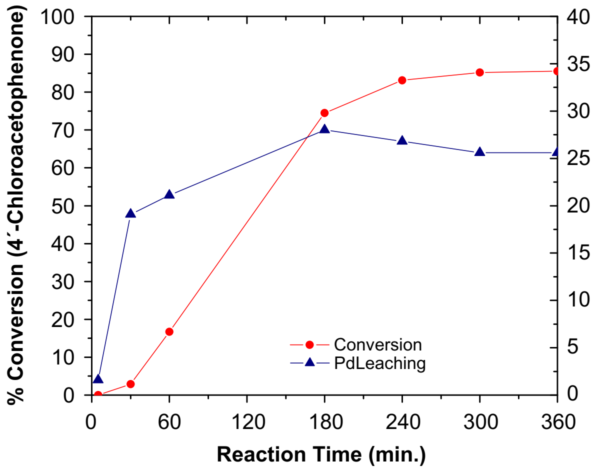


Fig. 5. Correlation of Pd leaching and conversion in the Suzuki reaction of 4′-chloroacetophenone with phenylboronic acid. Reaction conditions: 4′-chloroacetophenone (116 mmol, 1 eq.), NaOH (174 mmol, 1.5 eq.), TBAB (40 mmol), $PhB(OH)_2$ (128 mmol, 1.1 eq.), NMP:water 250:100 mL, 0.1 mol% of Pd (1% Pd/Al_2O_3), T = 65 °C, argon.

Analogous curves for palladium dissolution as function of reaction time have been observed for the Suzuki coupling reaction of 4′-chloroacetophenone with phenylboronic acid (Fig. 5). As expected for the lower reaction rate with the aryl chloride, the leaching curve is even broader, the amount of Pd in solution is lower (maximum 25% of total Pd) and re-deposition is far less efficient (higher amounts of Pd remain dissolved) for the aryl chloride compared to aryl bromides. We interpret this as an effect of mainly TBAB, which is a mandatory additive for the reaction. TBAB causes substantial amount of Pd leaching (see Section 3.3) and is not consumed during the reaction, thus avoiding the Pd re-deposition process.

In addition to temperature and conversion, the influence of various reaction parameters on the palladium leaching that are different for Suzuki and Heck reactions (temperature, boronic acid/styrene, solvent (mixture), base, etc.) can be expected. That is the reason why we performed a number of additional experiments

Table 3
Effect of different reagents on the palladium leaching under mild reaction conditions.

Entry	Solvent(s)	Additives, substrates	% of total Pd in solution
1	NMP	–	2
2	H_2O	–	0
3	NMP/H_2O	–	8
4	NMP/H_2O	Na_2CO_3	38
5	NMP/H_2O	PhBr	12
6	NMP/H_2O	Na_2CO_3 + PhBr	29
7[c]	NMP/H_2O	$PhB(OH)_2$	–
8[c]	NMP/H_2O	$Na_2CO_3 + PhB(OH)_2$	–
9	NMP/H_2O	NaOH	7
10	NMP/H_2O	TBAB	47
11	NMP/H_2O	AcPhCl	10
12	NMP/H_2O	NaOH + AcPhCl	18
13[a]	NMP/H_2O	PhBr	5
14[b]	NMP/H_2O	PhBr	6
15[a]	NMP/H_2O	AcPhCl	6
16[b]	NMP/H_2O	AcPhCl	6

Conditions: The quantities used here are the same as used in the original Suzuki coupling reaction. NMP (5 mL), H_2O (2 mL), ArX (2.9 mmol), Na_2CO_3 (3.2 mmol), TBAB (1 mmol), $PhB(OH)_2$ (3.2 mmol), 0.0029 mmol Pd (1% Pd/Al_2O_3).

[a] Calcined catalyst.

[b] Reduced catalyst.

[c] Palladium black formation.

on the influence of a variety of reaction parameters on the dissolution of palladium from the surface (see Section 3.3).

3.3. Palladium leaching as function of reaction parameters

Table 3 summarizes experimentally determined palladium concentrations observed in the suspensions of the Pd/Al_2O_3 catalyst and other additives. In all leaching experiments, the mixtures were stirred at 65 °C for 1 h (i.e. the time when almost maximum palladium leaching has been observed during the Suzuki reaction, Fig. 3). The palladium content in the liquid phase was determined by AAS (all numbers are mean values of repeated measurements).

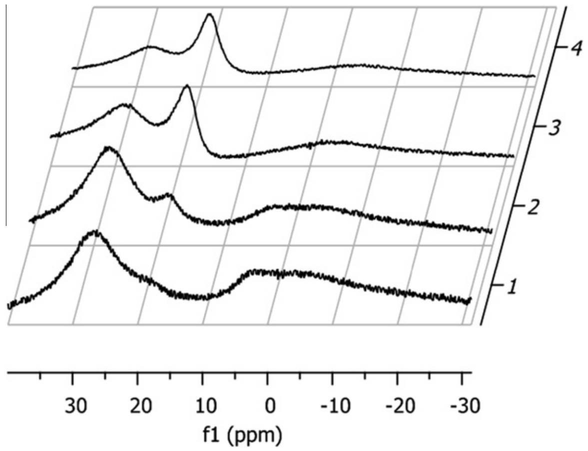


Fig. 6. ^{11}B NMR spectra of the reaction mixture recorded at different reaction times. (1) Stirring the reaction mixture at RT for 30 min without catalyst. (2) After adding catalyst, reaction mixture heated to 65 °C, reaction time: 5 min. (3) Reaction time: 35 min. (4) Reaction time 65 min.

Palladium leaching varies depending on solvent and on presence or absence of additives (base, TBAB) and substrates (aryl halides, phenyl boronic acid).

3.3.1. Influence of the solvent (water, NMP, mixtures)

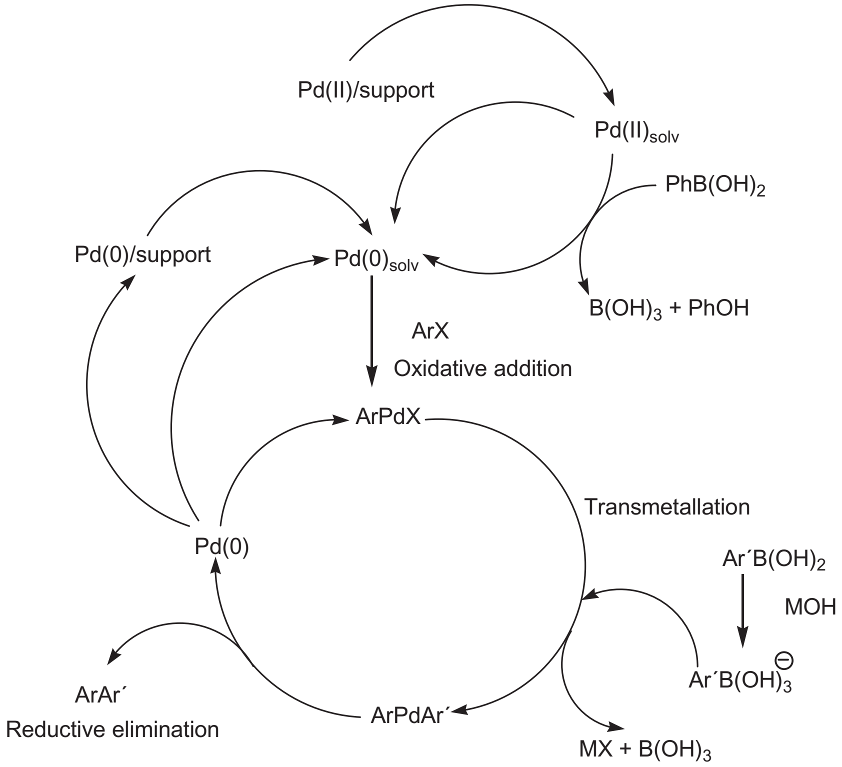
No palladium was detected in water. The concentration of Pd dissolved in NMP (2%) and in NMP/water mixtures (8%) is very low. Obviously, some but only very low amounts of Pd can be dissolved by chosen solvents under given conditions.

3.3.2. Influence of additives (base, TBAB)

The presence of TBAB (47% palladium leaching) as well as the base sodium carbonate (38% palladium leaching) gives rise to substantial dissolution of Pd from the support. This is in good agreement with the observation that base and TBAB play a crucial role for an efficient catalytic protocol of Suzuki coupling reactions, in particular for more difficult substrates (aryl chlorides, Fig. 2). It explains also why the re-deposition of Pd is less efficient in Suzuki coupling reaction of 4′-chloroacetophenone (Fig. 5). It should be noted here that the present results concern experiments at 65 °C. The influence of base and temperature on Pd leaching has been reported in literature for Heck reactions at higher temperatures [57].

3.3.3. Influence of the substrates (aryl halide, $PhB(OH)_2$)

Mixing of phenylboronic acid with the catalyst in NMP/water resulted in visible palladium black formation under given conditions, indicating agglomeration of leached palladium species (Table 3, entry 7). This implies that considerable palladium leaching occurs into solution due to phenylboronic acid. In the absence of additional substrates (e.g. bromobenzene), the leached palladium species agglomerate to form palladium black. This is expected to occur due to subsequent dissolution, reduction (to Pd(0)) and agglomeration of palladium. Accordingly, Pd stabilized in solution by the base Na_2CO_3 forms palladium black if phenylboronic acid is additionally



Scheme 2. Catalytic cycle of Suzuki cross-coupling reactions catalyzed by supported Pd catalysts at mild reaction temperatures deduced from leaching experiments and ^{11}B NMR studies in this paper.

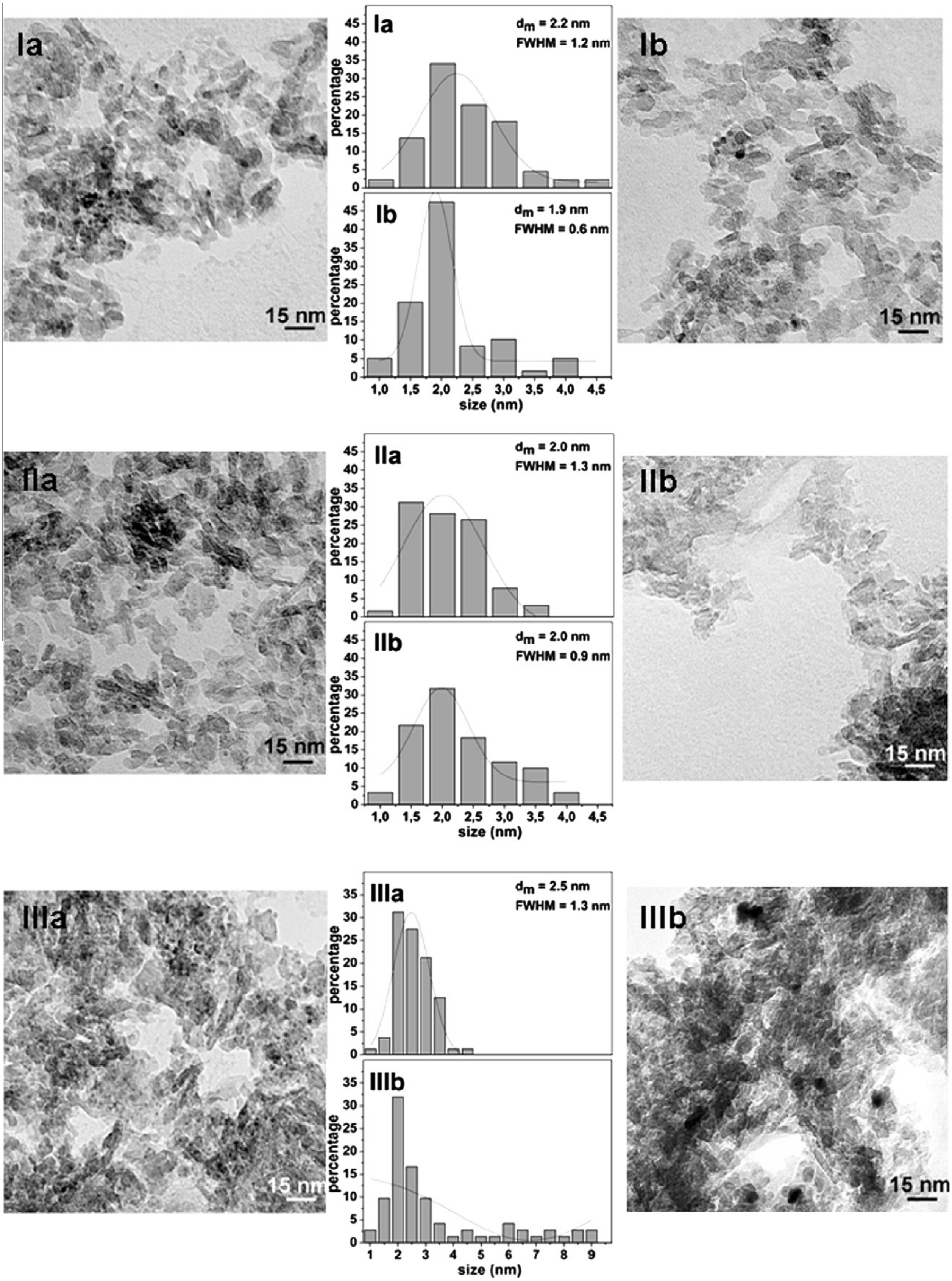


Fig. 7. TEM pictures of the Pd/Al_2O_3 catalysts with different initial palladium loading, before (left column) and after (right column) the Suzuki coupling reaction (for reaction conditions and yields see Table 4), showing nearly uniformly dispersed palladium nanoparticles (exception: IIIb). Pd particle size distributions are shown in the middle column. (Ia) 0.6% Pd/Al_2O_3 fresh catalyst, (Ib) 0.6% Pd/Al_2O_3 after reaction, (IIa) 2.0% Pd/Al_2O_3 fresh catalyst, (IIb) 2.0% Pd/Al_2O_3 after reaction, (IIIa) 5.0% Pd/Al_2O_3 fresh catalyst, (IIIb) 5.0% Pd/Al_2O_3 after reaction.

present due to reduction of Pd(II)–Pd(0) (entry 8). Pd leaching in the presence of phenylboronic acid has recently been noticed (not quantified) in Suzuki reactions catalyzed in the presence of Pd/C [34]. Pd leaching in the presence of either bromobenzene (12%) or 4′-chloroacetophenone (10%) is rather low and very similar in both cases. Simultaneous presence of aryl halide and base (entries 6 and 12) results in increased Pd leaching in comparison with that observed for the aryl halide alone (entries 5 and 11, respectively).

3.3.4. Influence of the catalyst pre-treatment

Thermally treated catalyst showed lower Pd leaching in the presence of bromobenzene (entries 13 and 14) or 4′-chloroacetophenone (entries 15 and 16) when compared to that observed in the presence of simple air-dried catalyst (entries 5–11, respectively). The observation is in agreement with the higher activity of air-dried catalysts for the Suzuki coupling reactions when compared to the thermally treated catalysts (Section 3.1).

The experimental results demonstrate that all factors that influence the catalytic activity (substrates, additives, base, and solvent) affect the Pd leaching in Suzuki coupling reactions, however, to clearly different extent. Whereas very low or no leaching is observed in pure solvents at 65 °C, addition of base or TBAB brings around 40–50% of the total palladium present in the system into solution. Aryl halides alone cause very low Pd dissolution. They play however a crucial role in combination with phenylboronic acid. The latter causes substantial leaching of palladium accompanied by reduction and subsequent formation of palladium black. If however both substrates are present, Pd(0) species in solution formed by the phenylboronic acid convert the aryl halide and are not precipitated as palladium black. The influence of the various parameters that influence Pd leaching during the reaction is in good principle agreement with parameters to be optimized for an efficient reaction protocol underlining the important role that Pd leaching plays for Suzuki reactions with supported catalysts. In addition, these results explain why different (and sometimes seemingly contradicting) results are published in literature [46] concerning Pd leaching and homogeneous or heterogeneous nature of the reaction. In fact, one can chose the reaction conditions where the Pd leaching can be suppressed nearly completely. Then, however, only modest and non-demanding substrates (i.e. aryl iodides or activated aryl bromides) can be converted that require only traces of Pd for activation.

3.4. ^{11}B NMR studies

Boron NMR studies were carried out in order to get additional information on the role of boronic acid in Pd leaching and in the reaction as a whole. Fig. 6 shows the ^{11}B NMR spectra of the samples taken from the reaction mixture (Suzuki coupling reaction of bromobenzene with phenylboronic acid under given conditions) at different intervals of time. Initially, the boron NMR spectrum of the reaction mixture was recorded without adding the catalyst. As shown in Fig. 6 (bottom), two main signals appear in the NMR spectrum: a relatively sharp signal (27.8 ppm) due to phenylboronic acid and a broader upfield signal (−1.0 ppm) representing a tetracoordinated boron [58] species generated in the presence of base. A new boron signal starts appearing at about 18 ppm, indicating the formation of $B(OH)_3$ [58] just after the addition of the catalyst (Pd/Al_2O_3). The immediate formation of $B(OH)_3$-like species implies the initial interaction of the noble metal with the boron species (generation of Pd(0) species) in the reaction mixture. As the reaction proceeds further, the signal for $B(OH)_3$ (18 ppm) grows quickly ($B(OH)_3$ formation via repeated transmetallation steps). At the same time, the signal of $PhB(OH)_2$ (around 27 ppm) decreases considerably. On the other hand, the intensity of the broad signal for tetracoordinated species remains almost constant.

The observations imply that phenylboronic acid reacts quickly with Pd^{II}/Al_2O_3 to produce boric acid ($B(OH)_3$) and possibly phenol (PhOH). At the same time, Pd^{II} is reduced to catalytically active Pd^0. In the presence of an aryl halide, these active species enter the catalytic cycle (oxidative addition). Alternatively, when no active substrate is present, Pd(0) species aggregate to give palladium black as observed in the Pd-leaching tests (see Section 3.3). $B(OH)_3$ (18 ppm) is continuously generated in the transmetallation step of the catalytic cycle with consumption of $PhB(OH)_2$ (27 ppm). The speculated catalytic cycle is depicted in Scheme 2. The assignments in ^{11}B NMR experiments have been deduced from the previous literature reports [59].

3.5. TEM characterization of the catalyst before and after Suzuki coupling reactions

The experimental results described in Section 3.2 (Fig. 3) clearly show that the Suzuki coupling reaction of bromobenzene involving supported catalysts is accompanied by Pd dissolution–re-deposition processes. The question arises whether the reaction affects the morphology and dispersion of the palladium particles on the surface of the support. Fig. 7 represents TEM figures of fresh and spent catalysts with different palladium loadings (0.6 wt.%, 2 wt.%, and 5 wt.% Pd/Al_2O_3, respectively) used in Suzuki coupling reactions. Due to controlled immobilization procedures [47] (identical in all cases), the fresh catalysts (Fig. 7, left) exhibit a high Pd dispersion and uniform particle size distribution. This uniform distribution of particle sizes can also be observed in the used catalysts (Fig. 7 Ib and IIb), where almost 100% of the aryl bromide was converted into the desired product (see Table 4, entries 1 and 2). The close observation of Fig. 7 IIa and IIb (2 wt.% Pd) indicates that the particle size distribution is even slightly improved in the spent catalyst compared to the fresh catalyst. This is important for the desired reusability of the catalyst. In contrast, the TEM figures of 5% Pd/Al_2O_3 (IIIa and IIIb) indicate that the initial uniform particle size distribution in the fresh catalyst is destroyed after the reaction. Similar observations have been reported for 5 wt.% Pd/C catalysts used in Heck reactions [29]. This illustrates the remarkable influence of palladium loading on the properties of the catalysts being relevant for recycling and reuse. Catalysts with higher Pd loadings leach more palladium into the solution. Higher total Pd concentrations in solution at a given time lead to less-controlled re-deposition process. This results in the decrease in Pd dispersion during the reaction, leading to a significant decrease in the catalytic activity (50% conversion in 5 h, see Table 4, entry 3 vs. 80%

Table 4
Particle size distribution of palladium on alumina catalysts.

Pd/Al_2O_3 loading (%)	Aryl halide: conditions	Reaction yield	Nanoparticle size (nm) determined from TEM	
0.6	PhBr: NMP:water, Na_2CO_3, 0.1 mol% Pd, 65 °C, 6 h	99%	Fresh catalyst	2.2 ± 1.2
			After reaction	1.9 ± 0.6
2.0	PhBr: NMP:water, Na_2CO_3, 0.11 mol% Pd, 65 °C, 6 h	100%	Fresh catalyst	2.0 ± 1.3
			After reaction	2.0 ± 0.9
5.0	MeOPhBr: NMP:water, Na_2CO_3, 0.1 mol% Pd, 65 °C, 5 h	53%	Fresh catalyst	2.5 ± 1.3
			After reaction	3.3 (No uniform distribution)

conversion in 4 h, see Table 2, entry 4). It can be concluded that the re-deposition process can be controlled by choosing the right catalyst (higher surface to metal ratio) and a carefully optimized reaction protocol. This concept can efficiently be used to improve the catalyst activity as well as reuse of the supported catalysts for practical applications. The results also clearly demonstrate that unchanged particle size distribution cannot be considered as a criterion for the heterogeneous mechanism of the reaction as has been claimed in some articles related to Suzuki reactions [30,60].

4. Conclusions

Supported palladium catalysts like Pd/Al_2O_3 prepared by controlled precipitation of Pd(II) salts are highly active and selective catalysts for Suzuki cross-couplings of aryl bromides and activated aryl chlorides under mild reaction conditions (65 °C, NMP/Water). Thermal treatment and reduction of the catalyst at higher temperatures cause substantial loss of activity. Palladium leaching during the reaction correlates directly to the progress of the reaction. Corresponding dissolved molecular palladium species are the active species in the reaction and a prerequisite for high activity and selectivity. Palladium leaching and conversion of the aryl halide starts at rather low (even at room) temperature showing potential of the reaction at low temperatures. The palladium amount in solution depends in a complex manner on a variety of parameters. Base, additives, boronic acid, and substrates differently contribute to palladium leaching. Temperature plays a crucial role in Pd leaching, there is however no single linear dependence. For instance, higher temperatures force reduction to Pd(0) as well as precipitation of palladium. Thus, leaching at these higher temperatures is more difficult. Accordingly, different leaching mechanisms are expected and found for different regions of temperatures, substrates, and reactions (Suzuki, Heck).

Dissolved palladium species re-deposit onto the support at the end of the reaction. This re-deposition can be controlled by a variety of parameters. TEM investigations demonstrate that the Pd dispersion and particle size distribution on the support can be maintained or even improved by useful choice of catalyst (loading) and reaction parameters. Accordingly, a variety of tests (like Pd analysis of the filtrate or the analysis of the heterogeneous catalyst after the reaction) demonstrating the heterogeneous character of the catalytic cycle proposed and performed in the literature cannot be regarded as sufficient. Also, for more accurate Pd-leaching investigations, care should be taken in choosing the right reaction parameters (and the substrates) for heterogeneous coupling reactions. The investigations contribute to the understanding of leaching and the nature of the active Pd species in heterogeneous systems as a relevant prerequisite for the knowledge-based development of the new Pd catalysts.

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