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Suzuki Coupling Reactions in Neat Water as the Solvent: Where in the Biphasic Reaction Mixture Do the Catalytic Reaction Steps Occur?

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Abstract: Many reports on water-compatible palladium catalysts have appeared in the recent literature. For hydrophobic substrates, mixtures with pure water are biphasic, and it is widely not regarded that the elusive locality of the catalytic process (in water, the organic layer, or at the phase boundary) has an important impact on the mechanism and efficiency of the reaction. In the present work, for the first time systematic variation of reaction parameters has been performed for Suzuki coupling experiments with chloro- and bromoarenes in pure water. The investigations are not only aimed at the factors influencing the catalytic activity, but also at the effects that may occur particularly in water/organic biphasic media, and on the question as to in which of the two liquid phases the reaction takes place. These investigations have revealed that dilution of the base (in the aqueous layer) and the Pd species (in the organic layer) are detrimental to the reaction, and that phase-transfer processes play a major role in the overall mechanism. A series of experiments with variation of parameters like precatalyst hydrophilicity, organic and water phase volume, additives, stirring rate, base concentration, and so forth, indicate that for the systems under study the reaction occurs in the organic layer. The water phase needs to be present to dissolve and provide polar reactants, and re-absorb side products. The results encourage to pay more regard to the question of phase locality of coupling reactions in water in general.

Keywords: biphasic catalysis · C–C coupling · palladium · Suzuki reaction · water

Introduction

While for a long time water has mostly been banished from organic synthetic protocols, it has recently become popular again as a solvent for synthetic reactions in light of the search for "green" chemical processes. Water is a very cheap and the most environmentally benign solvent, as it is abundant in nature, and nonhazardous (inflammable, nontoxic). It also possesses a strong solvation ability especially for polar and ionic substances. In turn, this also implies that nonpolar substances, which represent the major part of reactants and products for reactions in organic synthesis, are not miscible with water and will cluster or separate to build a second liquid or solid phase. Hydrophobic reaction products can, thus, be easily separated by filtration or phase separation, while polar side products, especially saline products, are carried away with the water phase.

In recent years, a surprising accelerating effect has also been observed when reactions between water-immiscible reactants were performed under stirring with water. This effect has led to the new field termed "on-water chemistry".[1] Aside from the ground-state destabilization of hydrophobic reactants in water, the accelerating effect has been explained by the large cohesive energy density of water resulting in a compression of organic reactants.[2] This hypothesis has been replaced recently by the explanation that free "dangling" O−H bonds at the phase boundary are able to stabilize the transition state of some reactions, leading to increased reaction rate and even altered and increased selectivity.[3]

Pd-catalyzed C–C cross-coupling reactions, like, for example, the Suzuki–Miyaura coupling of aryl halides and organoboronates, represent a modern means for the versatile regioselective and stereospecific synthesis of larger and complex molecules from prebuilt and prefunctionalized precursors. Since their discovery in the 1970s, these reactions have found manifold applications in organic synthesis and fine chemical production, and their development was recently awarded with the Nobel prize. As C–C coupling reactions include the presence of organometallic species (organopalladium intermediates), exclusion of water from these reactions seems mandatory. However, it is found that water behaves as a poor nucleophile in C–C coupling reactions,[4] making it suitable as a solvent or cosolvent. In fact, especially the Suzuki–Miyaura reaction has for a long time been performed under aqueous conditions or in water alone,[5,6] and was found to benefit from the presence of water.[7]

When nonpolar hydrophobic reactants are applied, Suzuki reactions in water actually occur in a biphasic medium

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(water + organic reactants and products). Thus, water may not actually be a real "solvent" for this reaction, and the reaction does not take place "in" but rather on water. This is widely unregarded in publications about Suzuki coupling in water or water-containing solvent mixtures; it seems to be assumed that at least some small part of the reactant is somehow dissolved in water and will react. In this work, such reactions will nevertheless be regarded as reactions "in water" or "with water as the only solvent", to avoid confusion among many different terms.

The biphasic nature of such Suzuki reaction mixtures raises the question as to whether the actual reaction mainly takes place in the water phase, the organic phase, or at the phase boundary. Qualitative arguments in favor and against any of these cases can be thought of (Table 1). The answer as to where the reaction takes place has important consequences. If the reaction takes place in the organic layer, the reactant is the "solvent", which influences all the manifold and intricate processes occurring during C–C coupling catalysis (side reactions, solvation of intermediates, deactivation of Pd through agglomeration, and many more). The delicate interplay of these processes may significantly be changed when going from one substrate to another chemically different substance. Moreover, the reactant "solvent" is consumed and replaced by the (also chemically different) product as "solvent", having similar consequences.

Table 1. Factors affecting the locality of the catalytic process of Suzuki coupling in biphasic reaction mixtures (water/organic reactants).

Phase	Present species	Favorable	Unfavorable
water	base, phenyl boronate, salts, ionic Pd species	presence of boronate, stabilization of ionic species including saline side products	low/no availability of reactant, decomposition reactions
organic	reactant, product, neutral and ionic Pd species, free phenyl boronic acid	excess of reactant, no/weak solvation of ionic species	"clustering" of ionic species
phase boundary	all	availability of all components	diffusion limitations, constricted mobility

On the other hand, if the reaction takes place in water, the aqueous phase can be reused after removing the hydrophobic products and adding new reagents, at least until the cumulated amount of saline side products in the water phase stalls the catalytic activity. The products would then also contain no or only very low amounts of Pd, making further time- and material-consuming purification processes unnecessary, such as, for example, for pharmaceutical products, the heavy metal contents of which must meet very low law-enforced restrictions.[6] If the reaction takes place in water, however, this also implies that the reaction rate is limited by the low concentration of the hydrophobic reactant in the aqueous layer, which has been observed in some cases in the literature (see below).

The locality of the reaction also has a strong impact on possible ways to develop and optimize catalytic systems and reaction conditions for higher activity and efficiency in reactions in pure water. All of these considerations may also apply to aqueous solvent mixtures (water/alcohols), which have also been widely applied for the Suzuki reaction, and also give biphasic reaction mixtures. Nevertheless, the focus of this work is on the use of only water.

Although there is a vast amount of available publications on the Suzuki reaction in (pure) water, the biphasic nature of the reaction mixture and the question of the reaction's locality are widely unregarded, and a clear answer is still missing. Mostly, Pd complexes as the homogeneous catalyst have been tailored to be water-compatible (i.e., soluble) for higher activity.[6,8–10] Some Pd complexes have been found to decompose under the reaction conditions, which has been observed also for very stable precursors,[11,12] thereby generating the actual catalytically active free Pd^0 species, which is likely to be transferred into the organic layer for the major part. In other words, a water-soluble precatalyst does not necessarily lead to the active species also being dissolved in the water phase. This is practically never considered in the mentioned cases. Because of binding Pd^0 very strongly and therefore being part of the active species, P ligands can be regarded as a typical exception for this phenomenon (under mild reaction conditions). In some work, low reaction rates have, however, been observed for hydrophobic reactants in comparison to comparable hydrophilic substrates.[13] To overcome the miscibility "problem" detergents and co-solvents have been used,[14] as well as Pd complexes or particles in conjunction with amphiphilic, micellar polymers.[15] On the other hand, occasionally fast reactions of hydrophobic substrates have been observed with Pd on hydrophobic supports,[16] namely active carbon.[17,18] Overall however, there seems to be no clear trend as to whether hydrophilicity or lipophilicity of a reactant, catalyst, or support is beneficial; it may depend on the respective example.

As stated, the question as to whether the catalytic cycle occurs in the aqueous or the organic layer is of fundamental importance, but is widely unregarded. We have conducted and present here experiments on the Suzuki coupling of hydrophobic bromo- and chloroarenes in water, by using different catalyst precursors, to achieve insight into the locality of the catalytic process, and get useful information on a possible optimization of the reaction conditions. This is the first time such systematic investigations into the details of the phase distribution of the reactants, and their influence on the reaction and its mechanism, have been conducted. The experiments will be interpreted in light of the question in which of the two liquid phases the reaction occurs. In the present work, we hope to bring this question into the minds of researchers working with different aspects (synthesis, catalysis design, reaction mechanisms, kinetics) in this field.

Results and Discussion

Preliminary experiments:

Distribution of reactants, catalyst, and products into the liquid phases: In contrast to typical mechanistic investigations in the literature, it has been conclusively decided to apply demanding substrates, such as aryl chlorides and deactivated aryl bromides for the present investigations. This should avoid misinterpretations due to the action of highly active traces of Pd, as observed previously for aryl iodides and activated aryl bromides.[11b] Only if it is believed to be particularly useful (in order to verify that even activated aryl bromides do not react under the specific conditions) activated aryl bromides have been applied. Though a (very small) partial solubility in the aqueous layer (intricately influenced by temperature and dissolved ionic species) cannot be totally excluded, all introduced substrates are clearly hydrophobic and therefore always resulted in complete and fast phase separation.

Systematic variation of reaction parameters has been performed for the Suzuki reaction of aryl bromides and chlorides with phenylboronic acid in pure water.

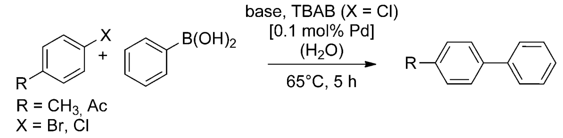
In the reaction mixtures, the base (NaOH or Na_2CO_3) is rapidly dissolved in water under stirring, and fast and quantitative formation of the boronate species $Na[B(Ph)(OH)_3]$ occurs. This species reduces free Pd^{II} to Pd^0.[19] The boronate is hydrophilic, so its concentration is high in the aqueous layer and low in the organic layer. Therefore the reduction of Pd occurs very fast when Pd resides in the aqueous layer, too, or is transferred to it (see below). This can be observed simply by adding a hydrophilic and a hydrophobic Pd^{II} compound (e.g., $Pd(OAc)_2$ and K_2PdCl_4) to a mixture of water and xylene or bromobenzene, and adding $Na[B(Ph)(OH)_3]$. The formation of Pd black is observed in the water layer of the solvent mixture in these experiments. This does, however, not necessarily imply that the Pd^0 species remain constrained to the water phase: if no specific ligands are applied that stabilize Pd^0 and are hydrophilic, Pd^0, be it the low-nuclear active species or Pd black, may actually be "free to go wherever it wants". This is even demonstrated by the simple experiment discussed here, in which the Pd black was highly capricious regarding its phase preference, and ended up residing in the aqueous layer, the organic phase, or staying at the phase boundary, unpredictably depending on the concentrations of each component and on whether heating was applied. Under the reaction conditions, a preference for the organic phase seems to prevail.[20] Considering that Pd (pre)catalysts can also decompose under the reaction conditions generating the catalytically active species,[11,12] the concept of making Pd catalysts water-soluble to increase their potential for coupling reactions in water cannot be taken to be generally valid.

The experiment also demonstrates that, unsurprisingly, water-soluble Pd^{II} compounds were more easily reduced than hydrophobic ones. In the experiments, K_2PdCl_4 was reduced quantitatively at room temperature shortly after the addition of the boronate, whereas $Pd(OAc)_2$ required heating and vigorous shaking to observe the formation of Pd black, and even then a residual yellow color of the organic layer indicated the presence of unreduced Pd^{II} species. Fast reduction of Pd^{II} also implies fast agglomeration and formation of Pd black, that is, deactivation of the catalytic species. In turn, the phase preference of the initial Pd^{II} compound should have an influence on the catalytic result. Thus, a variety of Pd compounds, soluble either in water or the organic layer, was applied as a precatalyst for the Suzuki reaction in water.

Effect of precatalyst hydrophilicity: Experiments were performed to investigate the influence of a Pd (pre)catalyst's phase preference (i.e., solubility in water or organic compounds) on the catalytic activity in the Suzuki reaction in water. A variety of hydrophilic and lipophilic Pd compounds were tested, including Pd^{II}phthalocyanine (PdPc), which had previously shown promising results in the (one-phase) Suzuki reaction.[12] A chelate complex of 8-hydroxyquinoline-5-sulfonic acid with Pd ($K_2[Pd(hqs)_2]$), the application of which as a catalyst for Suzuki coupling reactions of bromoarenes in water was recently published,[10] was also included in this study as a water-soluble counterpart to PdPc.

The precatalysts were applied in the Suzuki coupling of 4-bromotoluene or 4-chloroacetophenone in water at 65 °C. As the results in Table 2 show, the water-soluble precatalysts generally led to low yields. Better yields were obtained with

Table 2. Yields obtained in the Suzuki coupling of different substrates in water by using precatalysts of different phase preferences.



Precatalyst	Phase preference[a]	Yield 4-Me-biphenyl [%][b]	Yield 4-Ac-biphenyl [%][c]	Yield 4-Ac-biphenyl with excess base [%][d]
K_2PdCl_4	aq.	8	19	10
K_2PdBr_4	aq.	7	21	10
$K_2[Pd(hqs)_2]$	aq.	14	0	0
$PdCl_2$	ins./org.	11	25	60
$Pd(OAc)_2$	org.	13	18	4
$[Pd(acac)_2]$	org.	58	41	80
$[PdCl_2(PPh_3)_2]$	org.	73	9	13
PdPc	org.	26	10	6

[a] aq. = aqueous phase, org. = organic phase, ins. = insoluble. [b] Reaction conditions: 4-bromotoluene (3 mmol), $PhB(OH)_2$ (3.2 mmol), Na_2CO_3 (3.5 mmol), "Pd" (0.1 mol %), water (3 mL), 65 °C, 5 h, air. [c] Reaction conditions: 4-chloroacetophenone (3 mmol), $PhB(OH)_2$ (3.2 mmol), NaOH (4.5–4.8 mmol), TBAB (1 mmol), "Pd" (0.1 mol %), water (4 mL), 65 °C, 5 h, air. [d] As in [c], with 9–10 mmol of NaOH. acac = acetylacetonate.

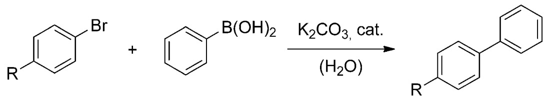
lipophilic precatalysts, but some of the lipophilic precatalysts also led to low yields (e.g., $Pd(OAc)_2$, or $[PdCl_2(PPh_3)_2]$ in the reaction with 4-chloroacetophenone). Thus, the activity of a precatalyst does not correlate primarily to its solubility or phase preference. This is especially demonstrated by the results for the coupling of 4-chloroacetophenone, in which the addition of tetra-*n*-butylammonium bromide (TBAB) transforms any of the water-soluble precatalysts into lipophilic ones (mainly by forming the salt $TBA_2[PdBr_4]$), but still low yields are observed for water-soluble and some lipophilic precatalysts.

The following aspects are considered to be determining the activity of a specific precatalyst: Firstly, as mentioned, water-soluble precatalysts are reduced faster than lipophilic ones, and in turn are also deactivated faster. Secondly, complexes of chelating ligands ($K_2[Pd(hqs)_2]$, $[Pd(acac)_2]$, PdPc) are reduced more slowly. Thirdly, the ligand (depending on its binding strength, chelating or monodentate nature) determines the release of Pd and, in turn, the generation of active Pd^0 species. Thereby it also determines the rate of deactivation of the active species.

In summary, the phase preference of a precatalyst is one, but not the determining factor for its activity. The activity is also determined by the complex's ability for Pd release under the respective conditions (temperature regime), the stabilization of the active species, and the prevention of deactivation.

Comparison of PdPc and PdTPP in the Suzuki coupling of aryl bromides: Table 3 shows the reaction results obtained in the Suzuki coupling of different aryl bromides with $PhB(OH)_2$ in water as the solvent. PdPc and Pd-*meso*-tetraphenylprophyrin (PdTPP), both only soluble in the organic reactant phase, have been applied as precatalysts. The reaction conditions chosen were identical to a previous report in the literature, in which a carboxylate-substituted water-soluble Pd^{II}tetraphenylporphyrin had been applied as the precatalyst.[9e] This ensured comparability of the obtained results and enabled a discussion on the effect of phase preference of the precatalyst on the reaction outcome.

Table 3. Catalytic results for the Suzuki coupling of aryl bromides with PdPc and PdTPP in water.[a]



Entry	R	Reaction time [h]	PdTPP Conversion ArBr [%]	Yield [%]	PdPc Conversion ArBr [%]	Yield [%]	Lit. yield [%][9e]
1	H	4	15	8[b]	77	81[b]	83
2	Me	4	30	<1	84	83	n.d.
3	MeO	4	0	0	78	78	80
4	CN	2	1	1	95	95	99
5	Ac	1	0	0	99	99	n.d.
6	NO_2	1	0	0	100	100	93

[a] Reaction conditions: aryl bromide (3 mmol), K_2CO_3 (6 mmol), $PhB(OH)_2$ (4.5 mmol), precatalyst (0.1 mol%), H_2O (3 mL), 100°C, air. [b] Listed yields may be higher due to oxidative coupling of $PhB(OH)_2$. n.d. = not determined

As can be seen, PdTPP was inactive as the precatalyst, and even in the case of highly activated 4-nitrobromobenzene no product formation was observed (Table 3, entry 6). Also, in other reactions only trace amounts or no products were observed. In contrast, PdPc was active as a precatalyst, giving the Suzuki coupling product in good to quantitative yields under these reaction conditions. The yields obtained with PdPc are almost identical to the literature yields derived under the same reaction conditions with a water-soluble Pd^{II}(tetraphenylporphyrin) (see Figure 1 for its structure).

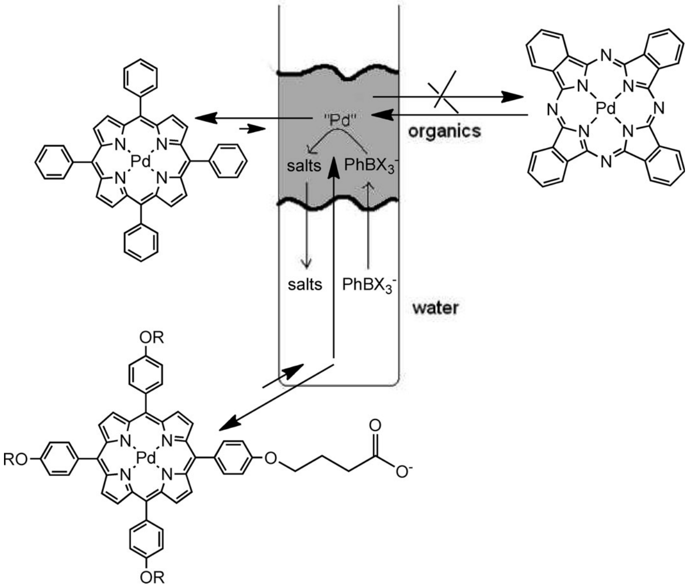


Figure 1. Proposed generation equlibria for free active Pd species in the Suzuki coupling of aryl bromides in water with Pd porphyrins and PdPc.

It has been observed in earlier work[12] that PdPc irreversibly releases Pd, which becomes the active species, whereas PdTPP reversibly releases only very low amounts of Pd and, therefore, does not generate enough active species in the solution. This is again reflected by its inactivity as a precatalyst in the Suzuki reactions described here. In contrast, a water-soluble porphyrin from the literature report had given rise to almost identical activity in comparison to PdPc. It cannot be presumed that the complex stability of a Pd porphyrin is significantly changed by peripheral substitution with carboxylate groups, nor that water as a surrounding medium leads to increased release of Pd from the porphyrin. In the latter case, PdTPP should have also been a good precatalyst for the Suzuki reaction in *N*-methyl pyrrolidone (NMP)/water mixtures, which has not been observed.[21] Instead, the observations can be explained by assuming that any Pd that is released into the water phase will irreversibly cross the phase boundary (Figure 1) and reside in the organic phase. In turn, the porphyrin in water is depleted from Pd, and the organic phase is continuously enriched with Pd, in a similar manner to when PdPc is used. Since the rate-determining step of the catalytic process is considered to be the phase transfer of the boronate and the transmetallation, which are independent from the Pd species, identical yields are then obtained under identical reaction conditions (see the Mechanistic Proposal section for a more detailed discussion).

Effect of stirring rate: To examine the influence of the phase transport and the interphase surface in more detail, experiments were performed by applying different stirring rates. No effect on the yields (Table 4) was found. It could be concluded that all phase transport (phenyl boronate, active Pd species, saline products) is in equilibrium as long as some stirring is applied, and therefore this is not limiting to the reaction rate. In addition, a reaction at the phase boundary, which should have been enhanced by stronger stirring, seems unlikely.

Table 4. Yields obtained in the Suzuki coupling at different stirring rates.[a]

Entry	Stirring rate [rpm]	Yield [%]
1	500	40
2	1000	36
3	1500	36

[a] Reaction conditions: 4-bromoanisole (30 mmol), $PhB(OH)_2$ (32 mmol), $K_2[Pd(hqs)_2]$ (0.1 mol%), Na_2CO_3 (35 mmol), water (30 mL), 80 °C, 3 h, air.

If not stirred, all of the reaction mixtures separate to give two distinct layers, without perturbation through boiling or convection. Reaction mixtures that were not stirred always led to lowered yields, which indicates a diffusion limitation of the reaction (see Table S1 in the Supporting Information).

Effect of the amount of base and water phase volume: The results for the reactions with 4-chloroacetophenone in Table 2 also demonstrate that, in most cases, higher yields are obtained when an excess of base is applied. This is in line with previous observations for Suzuki couplings in pure water by using heterogeneous catalysts.[17,18,22] The positive effect of an excess of base was specifically investigated for the reaction with 4-chloroacetophenone by using PdPc as the catalyst.

As Figure 2 shows, an excess (2–3 equiv) of NaOH was required for a quantitative reaction. Longer reaction times (4 h) did not lead to significantly higher yields, so the concentration of NaOH seems to be a limiting factor. Accordingly, when the volume of water was increased (NaOH is diluted), the yield decreased when low amounts of base (about 1.1 equiv) were used. With a threefold excess of base, this effect was no longer observed. Also, some amount of water was necessary for the reaction to occur, as in the absence of water only small amounts of the product were obtained (19% yield). It should be pointed out here that the beneficial effect of an excess or high concentration of base is not related to the formation of phenyl boronate. From the pK_a of phenyl boronic acid (8.86),[24] one can calculate that in all the experiments in Figure 2, >97% of phenyl boronic acid is present as (water-soluble) sodium phenyl boronate $Na[B(Ph)(OH)_3]$.[25]

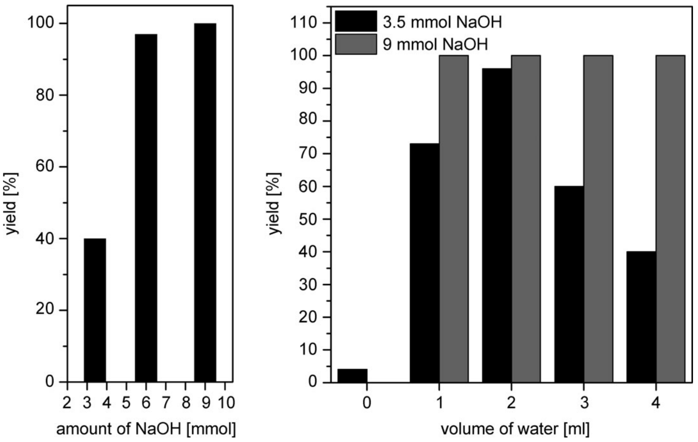


Figure 2. Effect of base amount and volume of the water phase on the yield of the Suzuki reaction in water: 4-chloroacetophenone (3 mmol), $PhB(OH)_2$ (3.5 mmol), TBAB (1.5 mmol), PdPc (0.1 mol%), NaOH (as specified), water (4 mL or as specified), 100 °C, 2 h, air. Reaction time was 1 h for experiments with 9 mmol of NaOH and the different water volumes.[23]

The effect of an increasing volume of the water phase was also investigated for three other reactions: the reaction of 4-chloroacetophenone with $[Pd(acac)_2]$ as the precatalyst at 65 °C, and the reaction of 4-bromoanisole with $[Pd(acac)_2]$ or $K_2[Pd(hqs)_2]$ at 80 °C (Figure 3). As the results show, the yield eventually decreased with an increasing amount of water in any of the experiments, when the amount of base is kept constant. This is again explicable by a dilution of the base being detrimental to the yield, although a minimum amount of water also appears to be necessary for thorough solvation of the reactants.

Test for on-water effects: Four reactions were also performed with D_2O instead of H_2O. As Table 5 shows, in comparison, similar or even clearly increased yields were obtained when using D_2O. This is an important result, as it reveals that the reaction does not benefit from the “on-water” effect men-

Table 5. Comparison of the yields for reactions in H_2O and D_2O.[23]

Catalyst	Aryl halide	T [°C]	Reaction time [h]	Yield in H_2O [%]	Yield in D_2O [%]
PdPc	4-chloroacetophenone	100	0.8	74	96
$[Pd(acac)_2]$	4-chloroacetophenone	65	5	40	79
$[Pd(acac)_2]$	4-bromoanisole	80	3	58	62
$K_2[Pd(hqs)_2]$	4-bromoanisole	80	3	60	55

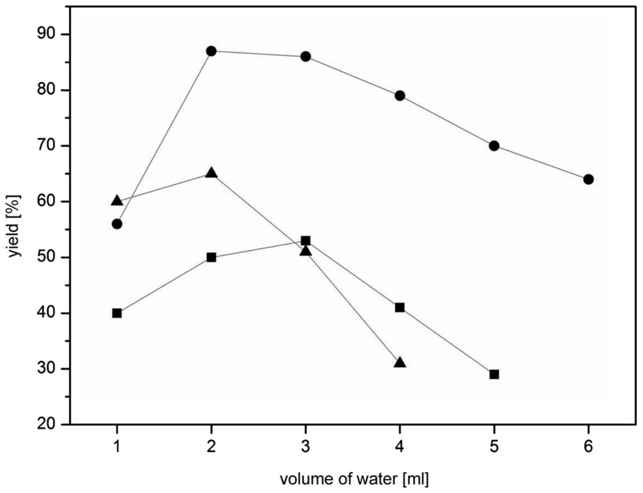


Figure 3. Effect of the water phase volume on the yield in the Suzuki reaction in water. ■ = 4-Chloroacetophenone (3 mmol), $PhB(OH)_2$ (3.2 mmol), NaOH (4.8 mmol), TBAB (1.0 mmol), $[Pd(acac)_2]$ (0.1 mol %), water (as specified), 65 °C, 5 h, air. ● = 4-Bromoanisole (3 mmol), $PhB(OH)_2$ (3.2 mmol), $[Pd(acac)_2]$ (0.1 mol %), Na_2CO_3 (3.5 mmol), water (as specified), 80 °C, 3 h, air. ▲ = 4-Bromoanisole (3 mmol), $PhB(OH)_2$ (3.2 mmol), $K_2[Pd(hqs)_2]$ (0.1 mol %), Na_2CO_3 (3.5 mmol), water (as specified), 80 °C, 3 h, air.[23]

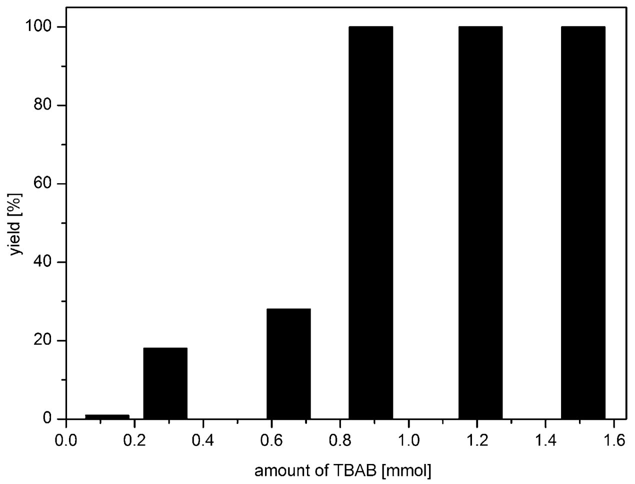


Figure 4. Effect of the amount of TBAB on the Suzuki reaction in water: 4-chloroacetophenone (3.0 mmol), $PhB(OH)_2$ (3.5 mmol), TBAB (as specified), PdPc (0.1 mol %), NaOH (9 mmol), water (4 mL), 100 °C, 2 h, air.

tioned earlier (see the Introduction). These effects are always lower in D_2O, which is a slightly better solvent for hydrophobic reactants than H_2O,[26] and therefore causes less destabilization. Instead of lowered yields[1] or longer reaction times[3] in D_2O, the opposite trend was observed. This could be explained by a lower or less efficient solvation and stabilization of the phenyl boronate in D_2O, making it more reactive or more likely to cross the phase boundary into the organic phase.

Effect of additives: The effect of typical additives on the Suzuki reaction was tested in the coupling of 4-chloroacetophenone by using PdPc, for which the addition of a minimum amount of TBAB was found to be mandatory (Figure 4). Generally, among the tetraalkylammonium salts, TBAB leads to the best performances in C–C coupling reactions,[27] and is considered to electrosterically stabilize palladium nanoparticles against agglomeration, thereby preventing premature formation of Pd black and, hence, deactivation.[11b,27–30]

TBAB has also been discussed to enhance Pd leaching from dissolved and supported nanoparticles, and to build stable and highly active low-nuclear bromo complexes of Pd.[30–34] Peculiarly for C–C coupling reactions with water or in similar biphasic mixtures, TBAB has often been stated to be needed as a phase-transfer catalyst.[35] It is, however, not clear as to why a phase-transfer catalyst would be needed for reactions with aryl chlorides, whereas aryl bromides could be effectively converted in biphasic mixtures without additive, as demonstrated in this work. Also, some examples of TBAB-free Suzuki reactions of aryl chlorides in water have been reported previously.[8,36]

Other additives (PEG2000, LiBr, [18]crown-6) also led to the reaction not occurring, as did the use of other bases (K_2CO_3, KOH, NaOAc, Cs_2CO_3) when TBAB was not present. The reaction was also performed with 2- and 4-chlorobenzonitrile as substrates, for which KF was used as a base instead of NaOH to avoid saponification of the nitrile groups. Though they are activated chlorides, and good reaction results had been observed with Pd/C under these conditions,[17,18] chlorobenzonitriles gave only very low conversions and yields with PdPc (not quantified), probably due to the change of base.

From these observations (Table 6), it is clear that TBAB is not solely a phase-transfer catalyst, although it may enhance phase transition processes during the reaction. It rather serves both as a catalyst stabilizer by shielding Pd nanoparticles from further agglomeration, thereby delaying

Table 6. Effect of different additives on the Suzuki reaction with 4-chloroacetophenone in water.[a]

Entry	NaOH [mmol]	Additive	Conversion [%]	Yield [%]
1	9.0	TBAB	100	100
2	9.15	TBACl	32	28
3	9.0	$TBAF \times 3H_2O$	13	6
4	9.2	tetra-*n*-heptylammonium bromide	99	99
5	9.3	tetra-*n*-octylammonium bromide	60	46
6	9.4	tetraphenylphosphonium chloride	2	2
7	9.12	tetramethylammonium bromide	<1	<1
8	7.95	tetramethylammonium hydroxide	0	0
9[b]	–	tetramethylammonium hydroxide	<1	<1
10	8.67	tetra-*n*-butylammonium hydroxide	53	51
11[c]	–	tetra-*n*-butylammonium hydroxide	71	71
12[d]	9.38	cetyltrimethylammonium bromide	22	22

[a] Reaction conditions: 4-chloroacetophenone (3 mmol), $PhB(OH)_2$ (3.5 mmol), additive (1.5 mmol), PdPc (0.1 mol %), water (4 mL), 100 °C, 2 h, air. [b] 3 mmol of additive were used. [c] 3.5 mmol of additive were used. [d] 1.0 mmol of additive was used.

the catalyst deactivation,[11b,27–30] and through the formation of stable bromo complexes of Pd.[30–34] It also provides activity-increasing counter-ions for anionic species (palladates, boronates[35b,38]) involved in the catalytic process.

Effect of organic-phase volume: If the reaction would proceed in the water phase, the hydrophobic substrate needs to diffuse into the water layer, where it reacts with Pd and the boronate species. The immiscibility of the substrate and water implies that the water phase is saturated with the substrate throughout the reaction. An increase of the amount of substrate should, therefore, not influence the yield, if all other parameters are kept constant. Experiments were, thus, performed in which the amount of substrate, that is, the volume of the organic layer, was varied.

Figure 5 shows the dependence of the yield (with respect to phenylboronic acid) on the volume of the organic layer.

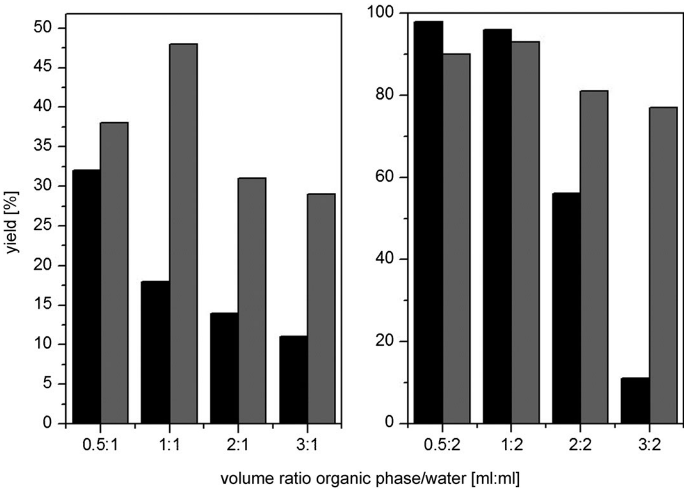


Figure 5. Effect of the volume of the organic phase on the Suzuki reaction in water. Yields are related to $PhB(OH)_2$: black left: $PhB(OH)_2$ (3.0 mmol), TBAB (1.0 mmol), NaOH (3.5 mmol), PdPc (0.1 mol%), 4-chloroacetophenone and water (volumes as specified), 100 °C, 2 h, air; black right: $PhB(OH)_2$ (3.0 mmol), TBAB (1.0 mmol), NaOH (4.7 mmol), $[Pd(acac)_2]$ (0.1 mol%), 4-chloroacetophenone and water (volumes as specified), 65 °C, 5 h, air; gray left: $PhB(OH)_2$ (3.0 mmol), Na_2CO_3 (3.5 mmol), $K_2[Pd(hqs)_2]$ (0.1 mol%), 4-bromoanisole and water (volumes as specified), 80 °C, 3 h, air; gray right: $PhB(OH)_2$ (3.0 mmol), Na_2CO_3 (3.5 mmol), $[Pd(acac)_2]$ (0.1 mol%), 4-bromoanisole and water (volumes as specified), 80 °C, 3 h, air.

As it can be clearly seen, the yield generally decreased, as the volume of the organic layer increased. This result is very indicative of the fact that the reaction does not proceed in the water phase! If so, the water phase would always have been saturated with the reactant, regardless of in how much of an excess it is present, and accordingly the yield would be identical.

In turn, assuming that the reaction takes place in the organic layer of the reaction mixture, the inhibitive effect of an increased volume of the organic phase could be attributed to the dilution of the active Pd species, thereby decelerating the (rate-determining) step of oxidative addition in the catalytic cycle.

Experiments were also conducted, in which the total volume of the reaction mixtures was kept constant (Figure 6). Water and aryl halide were added in different ratios, to give 4 mL in total. Given the observed effects, there would now be two opposing trends when going from "water-rich" to "water-poor" reaction mixtures: Whereas lower amounts of water lead to an increase of the yield (due to the higher concentration of base and boronate), an increasing organic phase volume leads to decreased yields. Accordingly, as Figure 6 shows, there is no absolutely clear trend observable for the yield of different reactions, when the phase volume ratio is altered. In reactions of 4-chloroacetophenone, the detrimental effect of an increased organic phase volume seems to prevail, as decreased yields are observed for water-poor mixtures. This effect is most pronounced for PdPc as a precatalyst. In contrast, reactions of 4-bromoanisole seem to give increased yields in water-poor reaction mixtures, although the trend is less clear than for chloroacetophenone.

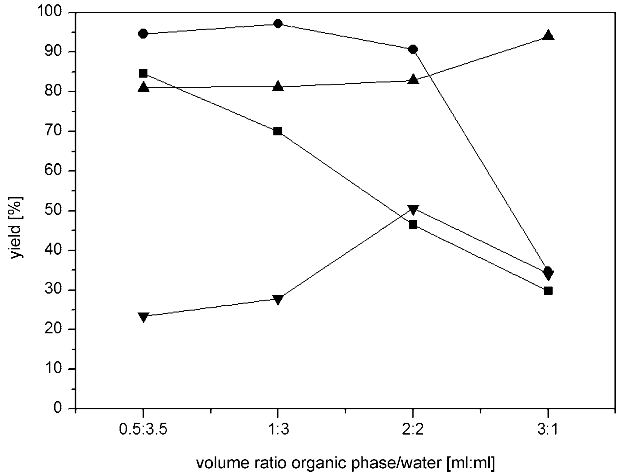


Figure 6. Effect of the organic phase/water phase volume ratio on the yield in the Suzuki reaction in water, keeping the total volume constant: $PhB(OH)_2$ (3 mmol), aryl halide and water as specified. ■ = 4-Chloroacetophenone, NaOH (9 mmol), TBAB (1.0 mmol), PdPc (0.1 mol%), 100 °C, 2 h. ● = 4-Chloroacetophenone, NaOH (9 mmol), TBAB (1.0 mmol), $[Pd(acac)_2]$ (0.1 mol%), 65 °C, 5 h. ▲ = 4-Bromoanisole, $[Pd(acac)_2]$ (0.1 mol%), Na_2CO_3 (3.5 mmol), 80 °C, 3 h, air. ▼ = 4-Bromoanisole, $K_2[Pd(hqs)_2]$ (0.1 mol%), Na_2CO_3 (6.0 mmol), 80 °C, 3 h, air.

Immobilization of a reactant in the organic phase: To further support the observations that the catalytic cycle takes place inside the organic layer, a polymeric halide was introduced as the reactant, since a polymer cannot freely dissolve into an aqueous phase. Conversion, thus, can only occur when the reaction occurs in the hydrophobic layer in which the polymer is free and active. Bromo-functionalized polystyrene was swollen in reactant-like organic solvents and reacted with phenylboronic acid in water (Table 7). As an indica-

Table 7. Bromopolystyrene as reactant.[a]

Entry	Organic solvent	Br content (blank test) [%][b]	Br content [%][b]	Conversion [%][c]
1	chlorobenzene	20	10	50
2	4-chloroanisole	20	8	60

[a] Reaction conditions: bromopolystyrene (2.5 mmol "Br"), $PhB(OH)_2$ (5.0 mmol), TBACl (1.0 mmol), $[Pd(acac)_2]$ (0.25 mol%), water (5 mL), organic solvent (5 mL) 100 °C, 24 h, air. [b] Br content determined by elemental analysis. [c] Calculated: ratio of the bromide content of the sample and of the blank test substrated from 100%.

tion of catalytic conversion, the bromide content of the polymer was compared with blank test samples (reaction without Pd), which indicated 50–60% conversion. Long reaction times and mediocre conversions are due to a reduced mobility and accessibility of the bromide functional groups in the polymeric network. Since the halide reactant is forced to reside in the organic layer, the catalytic cycle can only have occurred in the organic phase.

Summarizing discussion:

Mechanistic proposal for the Suzuki coupling in biphasic reaction mixtures: To explain the observed trends and effects, a summary of processes occurring during the catalytic reaction as depicted in Figure 7 is proposed, with the example of the reaction of 4-chloroacetophenone with PdPc as a precatalyst. The catalytic cycle is considered to take place in the organic layer (substrate). The reaction begins with PdPc dispersed in the organic layer, which generates the active Pd^0 species. The active species undergoes oxidative addition with 4-chloroacetophenone. As the overall concentration of the active species is low[12] and the oxidative addition of aryl chlorides is likely rate-determining, the concentration of the resulting Ar–Pd–Cl intermediate is also very low. An increase of the organic phase volume is then detrimental to the reaction due to further dilution of the active species, as observed (Figure 5).

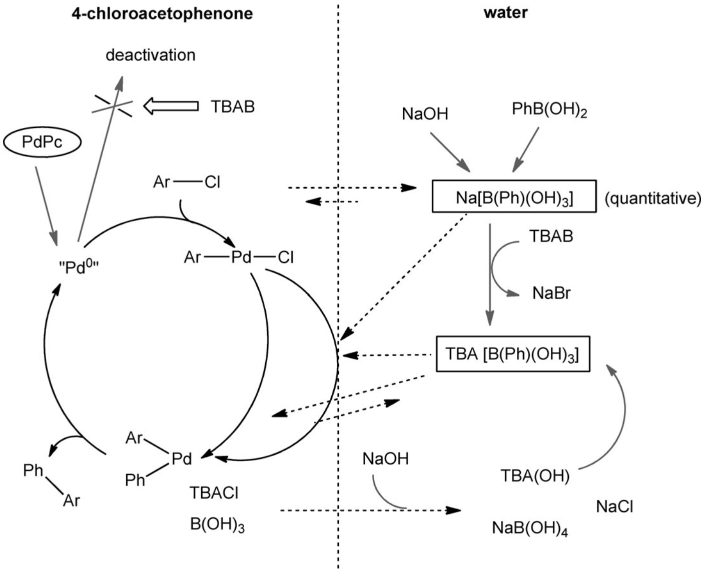


Figure 7. Proposal for the processes occurring during Suzuki coupling of 4-chloroacetophenone in water by using PdPc as a precatalyst. Black arrows indicate processes involved in the catalytic cycle, grey arrows (quantitative) chemical reactions, dashed arrows diffusion and phase-transfer processes.

In the aqueous phase, $PhB(OH)_2$ and NaOH quantitatively generate the boronate $Na[B(Ph)(OH)_3]$. The presence of a water phase is therefore mandatory to dissolve the solid NaOH and keep the boronate species dissolved, that is, reactive. This species has only a low tendency to cross the phase boundary and be dissolved in the organic layer. Through the presence of TBAB, ion exchange can occur to give $TBA[B(Ph)(OH)_3]$, which is more likely to be transferred into the organic layer, and is activated towards transmetallation. A similar effect has been attributed to PEG for the Suzuki reaction in a H_2O–PEG–$Pd(OAc)_2$ system.[39]

Because of the mentioned low concentration of the Ar–Pd–Cl species and the low concentration of the boronate species in the organic layer, the transmetallation step should become rate-determining as well, and activation of the boronate by TBA^+ is mandatory (Table 6).[35b,38] An excess of base may also enhance this process by "salting out" the phenylboronate. The phase transfer of the boronate is also enhanced when D_2O is used instead of H_2O, due to the decrease in stabilization by the solvent shell. This leads to a faster reaction (Table 5). On the other hand, the presence of fluoride ions may inhibit the phase transfer and/or the transmetallation step, thereby stalling the reaction, as observed in the case of chlorobenzonitriles (see section on additives).

For the reaction of aryl bromides the addition of TBAB was not necessary. Because of the higher reactivity of aryl bromides towards oxidative addition, the respective concentration of the Ar–Pd–Br intermediates is higher, and may be sufficient for the reaction to work also with the very low amounts of $Na[B(Ph)(OH)_3]$ present in the organic layer. In other words, while both oxidative addition and transmetallation are considered to be rate-determining in the case of aryl chlorides, for aryl bromides it may primarily be the transmetallation step. This is also in concurrence with obtaining identical yields by using different macrocyclic Pd complexes and rather similar results with different aryl halides (Table 3), if the Pd is in the organic layer and all other reaction parameters are identical, as the availability of the boronate depends on the reaction conditions and not the Pd source.

It can, however, not be ruled out that the transmetallation step takes place at the phase boundary, either in parallel or exclusively (Figure 7), although we consider it unlikely from the experiments showing no difference in yield when applying different stirring rates (Table 4). Both Na– or TBA–boronate species may be involved then, but the rate-enhancing effects of TBA^+ and D_2O and the inhibiting effect of fluoride remain similar.

Transmetallation generates the Pd–biaryl species, from which the coupling product and the active species are produced after reductive elimination. The active species enters a new catalytic cycle or deactivation pathways, the latter being inhibited by the presence of TBAB, as mentioned previously. The side products of the transmetallation, $B(OH)_3$ and TBACl, are transferred back into the aqueous layer, thereby also facilitating the transmetallation step. $B(OH)_3$ may consume a further equivalent of NaOH to create the corresponding water-soluble borate $NaB(OH)_4$, a process that may also be responsible for the necessity of an excess of base (Table 2 and Figure 2).

In summary, the reaction is proposed to take place in the organic layer, while the aqueous layer has an important supporting function, resulting in an efficient catalytic coupling reaction.

Conclusion

Suzuki reactions in biphasic systems by using only water as the solvent have been successfully performed in this work, and for the first time systematic investigations have been undertaken regarding the locality of the catalytic process. It has been demonstrated that the phase preference of the precatalyst is only one factor influencing the catalytic efficiency. The presence of a water phase and a high concentration of base were found to increase the yield. Among a variety of potent phase-transfer catalysts, TBAB was found to be the most efficient additive. An excess of the hydrophobic reactant led to lowered yields.

It is suggested that the reaction occurs inside the organic layer, while the water phase serves supporting and rate-enhancing purposes. With other reaction systems (reactants, catalysts), the situation may, however, be different, as the locality of the reaction will depend on several factors: the individual miscibility of the reactants and reagents with water, the ability of ligands to keep and stabilize Pd^0 species in water (expected for example, for sulfonated phosphane ligands), the pH, and the presence and effects of additives (detergents, polymers, etc.). In light of product separation and purification as well as catalyst reuse, a catalytic process taking place inside the aqueous phase is preferable. With this work, we hope to sensitize researchers in the field to pay regard to the biphasic character of C–C coupling reaction mixtures in water as the solvent. Future work to produce a broader understanding of the locality of C–C coupling reactions in biphasic reaction mixtures is highly encouraged.

Experimental Section

General: Catalytic reactions were, if not otherwise mentioned, performed in sealed glass tubes (45 mL) in a parallel synthesis unit (Radleys). After the respective reaction time, the reaction vessels were dipped into a water bath for 5 min to quench the reaction. Samples for reaction analysis were obtained by extraction with aliquots of H_2O/CH_2Cl_2, and drying the organic phase over $MgSO_4$. Substances were identified and quantified by gas chromatography (GC) on a Hewlett Packard HP 6890 equipped with a HP-1 column (100% dimethylpolysiloxane, bonded and cross-linked; length: 30 m, inner diameter: 0.25 mm, film thickness: 0.25 μm) as the stationary phase, nitrogen 5.0 (99.999 vol% purity) as the eluent gas, and a flame-ionization detector (FID). Diethylene glycol dibutyl ether (DEGBE) was used as an internal standard.

Suzuki coupling of 4-chloroacetophenone in water (standard procedure): Catalyst (0.1 mol% Pd), NaOH (4.5–9 mmol; added as pellet), phenylboronic acid (3.5 mmol), TBAB (1.0 mmol), DEGBE (150–250 mg as internal standard for GC analysis), and 4-chloroacetophenone (3.0 mmol) were introduced into a reaction tube. Water (3–4 mL) was added shortly before the reaction tube was placed into the heating source. The reaction was performed with vigorous stirring (800–1000 rpm) at 100°C for 2 h.

Suzuki coupling of 4-bromoanisole in water (standard procedure): Catalyst (0.1 mol% Pd), Na_2CO_3 (3.5 mmol), phenylboronic acid (3.2 mmol), DEGBE (150 mg as internal standard for GC analysis), and 4-bromoanisole (3.0 mmol) were introduced into a reaction tube. Water (3 mL) was added shortly before the reaction tube was placed into the heating source. The reaction was performed with vigorous stirring (800–1000 rpm) at 80°C for 3 h.

Suzuki coupling of 4-bromoanisole in water (experiments with different stirring rates): $K_2[Pd(hqs)_2]$ (0.1 mol% Pd), Na_2CO_3 (35 mmol), phenylboronic acid (32 mmol), DEGBE (1.60 g as internal standard for GC analysis), and 4-bromoanisole (30 mmol) were introduced into a two-neck-reaction tube. Water (30 mL) was added shortly before the reaction tube was placed into the oil bath. The reaction was performed with different stirring rates (500, 1000, 1500 rpm) at 80°C for 3 h.

Suzuki coupling of bromopolystyrene in water (polymeric reactant reaction): Bromopolystyrene (1 g; 2.5 mmol "Br") was placed in a reaction tube and swollen in the organic solvent (5 mL) for 12 h. Then $[Pd(acac)_2]$ (0.25 mol%), Na_2CO_3 (5.4 mmol), phenylboronic acid (5.0 mmol), and tetra-*n*-butylammonium chloride (1.0 mmol) were introduced into a reaction tube. Water (5 mL) was added shortly before the reaction tube was placed into the oil bath. The reaction was performed with vigorous stirring (800–1000 rpm) at 100°C for 24 h. After the reaction time, the reaction vessels were dipped into a water bath for 5 min to quench the reaction. The solvent was removed by filtration. The polymer was purified by washing exhaustively with water and CH_2Cl_2.

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