FULL PAPER

HELVETICA
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Impact of Solvent and Their Contaminants on Pd/C Catalyzed *Suzuki-Miyaura* Cross-Coupling Reactions

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Dedicated to Prof. *Antonio Togni* on the occasion of his 65th birthday.

The aim of this work was to understand if solvent contaminants can interfere in *Suzuki*'s cross-coupling reactions and if it can explain the lack of robustness in industrial processes. For this purpose, several parameters were tested on the industrial model reaction between 2-bromonaphthalene and phenylboronic acid catalyzed by Pd/C. Best results were obtained using THF as solvent. Traces of the precursors of the used solvents, such as 2,3-dihydrofurane or maleic anhydride (100–300 ppm related to the solvent) strongly poisoned the reaction, decreasing the conversion significantly. This means that to ensure robust production, solvent quality must be analyzed at the ppm level. Fortunately, addition of triphenylphosphine can circumvent the catalyst poisoning.

Keywords: cross-coupling, palladium on charcoal, poisoning, solvent effects, solvent contaminants, *Suzuki-Miyaura*.

Introduction

The selective and controlled formation of carbon-carbon bonds catalyzed by transition metals has been the most studied reaction in the last 40 years. Among these methods, the *Suzuki-Miyaura* cross-coupling (SMC), discovered jointly by *Suzuki* and *Miyaura* in 1979,[1,2] is certainly the most popular reaction for this type of chemical transformation. SMC is often used for the synthesis of conjugated dienes, higher polyene systems, and biaryls.[3,4] These systems are frequently found in active pharmaceutical and agrochemical ingredients.[5] In addition, polyaromatic molecules are regularly used as ligands, polymers and crystal liquids.[6,7]

In most SMCs, the catalysts used are palladium-phosphine complexes that are soluble in organic solvents. Thus, these homogeneous catalysts are rarely recoverable without elaborate and wasteful proce-dures, and therefore commercially expensive. More-over, phosphine ligands, which are toxic, may be more costly than the metal itself on an industrial scale.[8] In contrast, the use of Pd(OAc)$_2$ (which is easily reduced to Pd(0)[9]) or heterogeneous catalysis allows simple recovery and reuse of the catalyst.[10] In addition, the easy separation of the palladium catalyst from the reaction mass reduces the product contamination and water pollution with palladium. Nevertheless, hetero-geneous catalysts can suffer from limited mass transfer and leaching of the catalytic species from the surface of the support.[11] Another problem that may be encountered during catalysis is the loss of catalyst activity over time. This chemical and/or physical deactivation occurs simultaneously with the main reaction. Poisoning of the catalyst is one of these processes.[12] Among the catalyst used in heteroge-neous catalysis for cross-coupling, Pd/C is of growing importance, as it is easy to recover, available in bulk, and relatively cheap.[13] Indeed, activated carbon is inexpensive and widely commercially available. Under acidic and basic conditions, activated carbon is more stable than other supports like inorganic oxides.[14] In

addition, it has a much larger surface area than established supports such as alumina and silica.[14] Moreover, Pd/C can be burned to refine and recycle Pd.[15] Finally, Pd/C is a convenient phosphine-free catalyst for the *Suzuki-Miyaura* coupling.[16,17]

Recent development in the *Suzuki-Miyaura* cross-coupling reactions show that the catalysis is running well in biphasic medium or in water. In some cases, the SMC's performance is better in water or in water/solvent mixtures than only in organic solvent.[16,18] This is especially the case with nitrogen-containing heterocycles as substrate.[19] The use of water as solvent is particularly interesting as it is a cheap, non-flammable, non-toxic and abundantly available.[20] The use of Pd/C as catalyst in water or biphasic media make the SMCs a particular attractive method for industrial application, as it anchors this chemistry in sustainable and green process.

Although SMCs are very convenient for industrial application (mild reaction conditions, stability of boronic acids and their commercial availability, tolerance to a wide variety of functional groups and to the steric hindrance of substrates),[7,21] the choice of base, and solvent, and the absence or the presence of oxygen influences the outcome and the robustness of a given reaction.

Indeed, solvents can activate precatalysts, stabilize catalysts and reagents by coordination, modulate the reactivity of boronic acids and bases as well as influence the reaction selectivity and rate.[22,23] They also influence in some cases the separation of products and by-products.[23] Finally, several studies have reported the importance of solvent selection for Pd-catalyzed cross-coupling reactions[22–24] or the possibility of deactivation (due to coking)[25] or poison the Pd catalyst,[26,27] but – to the best of our knowledge – there are no current reports on the effect of solvent impurities and precursors in Pd/C-catalyzed reactions. Nevertheless, solvent impurities (as alkenes, alcohols or other molecules) can also inhibit the catalyst and lower its efficiency and/or modify its selectivity.

Strong bases facilitate the transmetalation step and their efficiency depends on the chosen couple of solvent/base.[24] Bases also influence the leaching of palladium.[28]

Usually, oxygen promotes the undesired homocoupling of arylboronic acid, especially in the presence of an aqueous base.[29] This reaction is slow under neutral pH conditions but is rapid when the reaction is carried out under basic conditions. It is therefore important to carefully inertize the reaction medium. It is also possible that this homocoupling will take place during work-up if the boronic acid has not fully reacted and is in contact with air.[29] However, some aerobic and anaerobic SMCs do not show a significant difference in performance at room temperature, which means that this phenomenon is certainly dependent on the operating conditions.[3]

Addition of PPh_3 as ligand has demonstrated to improve the kinetic of SMC catalyzed by Pd/C[29] probably due to the increase of soluble palladium during the reaction.[28] However, it has been observed that the phenyls bound to phosphine can participate in the cross-coupling reaction with aryl halides instead of boronic acid.[29] This side reaction is more pronounced with electron-rich and sterically unhindered halogens. This exchange is therefore favored in the case of substitution of the phosphine or aryl halide by an electro-donating group, whereas an electro-attracting or *ortho*-position substituent reduces this reaction.[29]

In this article, we examine the influence of base, solvent and their impurities on the conversion of the *Suzuki-Miyaura* cross-coupling catalyzed by Pd/C in biphasic conditions, using initially CPME as green solvent (*Scheme 1*).[30,31] This study will give means to improve the robustness of SMCs during scale-up and production at industrial scale.
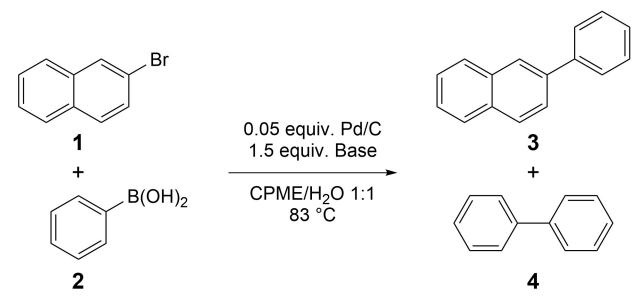
Results and Discussion

Bromonaphthyl **1** was used as an industrial model for the cross-coupling reaction with phenylboronic acid, catalyzed by Pd/C in a biphasic system (water/solvent, 1:1; *Table 1*). The main side-products of this reaction are the homocoupling products, principally 1,1'-biphenyl **4** from the homocoupling of phenylboronic acid **2**. As representative industrial catalyst, Pd/C

R = H, Me, CF₃, OMe, NH₂, NO₂, COOH
R' = H, NO₂
R" = H, F, Cl, Me
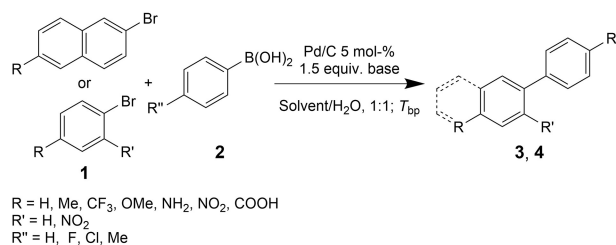
Scheme 1. Model reaction studied in this article: synthesis of 2-phenylnaphtalene 3 and the side-product 4 under typical reaction conditions (5 mol-% Pd/C, 1.5 equiv. of base, solvent/H₂O 1:1, at boiling temperature (T_{bp})).

Table 1. Synthesis of 2-phenylnaphtalene **3** using different bases with 5 mol-% Pd/C, 1.5 equiv. of base, 50 ml of CPME/H₂O 1:1, at 83 °C and under nitrogen. End of reaction after overnight (20–23 h).[a]

Base	Conversion of 1 [%]	3 [%a][b]	4 [%a][b]	Yield of 3 [%]
KF[c]	12.9	5.0	0.9	3.6
Na₂CO₃	29.6	21.2	5.5	25.1
K₂OH₃	35.1	19.5	6.3	23.6
KOH	43.1	27.2	5.6	34.1
CsOH	51.7	30.4	4.8	32.3
NaOH	51.3	37.6	7.1	36.9

[a] All the results are the mean of three trials, excepted for the KF (one trial). The conversion is calculated with the ratio between the concentration of the limiting reagent at time t and time t_0. [b] The 2-phenylnaphthalene and biphenyl purity is determined by HPLC (%a = %area). The yield is calculated based on the effective amount of the isolated products, corrected by HPLC purity. [c] Conversion after 6 h.

Noblyst P1067 from *Evonik* was chosen (10 % Pd on C, 50 % wet, *Degussa* type *E 101*).

The most commonly used bases in SMC (*i.e.* Na₂CO₃, K₂CO₃, NaOH, KOH, CsOH and KF) were tested to determine their influence on the reaction catalyzed by Pd/C, carried out in CPME/H₂O as solvent. Hydroxides gave better results than carbonates (*Table 1*). This phenomenon should be related to the fact that stronger bases promote the transmetalation step.[32] Additionally, it seems that global reaction rate decreases less quickly during the reaction with stronger base. When using carbonates as base, the reaction reaches a plateau after about 6 h, and the selectivity and purity are worse than hydroxide. The best conditions were found with sodium and cesium hydroxide (Conversion > 50%; *Table 1*). Sodium cation should favor the solubility in aqueous medium of the borate intermediate, which interact with Ar–Pd–Br in the transmetalation step. On the other hand, cesium cation can promote the transfer of the borate salt from the aqueous to the organic medium[33] affording

better conversion than the reaction performed with KOH.

In industrial processes the inertization conditions are normally applied principally as fire prevention measure, independently from the reaction type. Up to 6 to 8% *v/v* of oxygen can remain in the head-space of an inertized reactor.[1] Thus, the role of oxygen in this cross-coupling reaction was investigated, to understand its impact on conversion and on the formation of homocoupling side-products.[34] Two parallel trials were carried out: the first consisted in inerting the reactor and saturating the solvents with argon, and the second in saturating the solvents with air (*Table 2*). As expected, the purity of the final product, the selectivity as well as the conversion is lower in the reaction conducted under air. Indeed, the reaction stopped after six hours, indicating that the catalyst is poisoned by oxygen.[11] Additionally, the homocoupling product **4** increased significantly, in agreement with *Miller* and coworker's observations (*Table 2*).[34] Furthermore, complete absence of oxygen is difficult to achieve by simple vacuum/argon cycles. As a consequence, homocoupling side-product was detected also in the 'inertized' trial, due to the oxidation of Pd(0) species to Pd(II) by residual oxygen (*Miller* reported that 3.3 ppm O₂ led to 0.18% homocoupling side product).[34]

To determine the influence of solvent[22] on the conversion of 2-bromonaphthalene **1** and phenylboronic acid **2** catalyzed by Pd/C, the solvents THF, 2-MeTHF, CPME and toluene were selected as they are commonly used in SMC in pharmaceutical production.[35] All the reactions were carried out under nitrogen at reflux temperature using NaOH as base (*Figure 1*). THF Showed complete conversion after 60 minutes and 83.8% yields of isolated product (mean on 3 trials, ±1.6%, *Table 3*) combined with excellent purity (96.2%) was obtained. Furthermore, the catalysis showed better selectivity and produced

Table 2. Synthesis of 2-phenylnaphtalene **3** using with 5 mol-% Pd/C, 1.5 equiv. of NaOH, CPME/H₂O 1:1, at 76 °C, under air and under Ar. End of reaction after 21 h.

Reaction conditions	Conversion of 1 [%]	3 [%a]	4 [%a]	Yield of 3 [%]
under Ar	51.3	37.6	7.1	36.9
under air	39.4	33.4	15.3	34.9

[1] *Helsinn*'s measurement in industrial 4000 L reactors after 2–3 cycles of vacuum (up to 100 mbar)/nitrogen (1 bar).
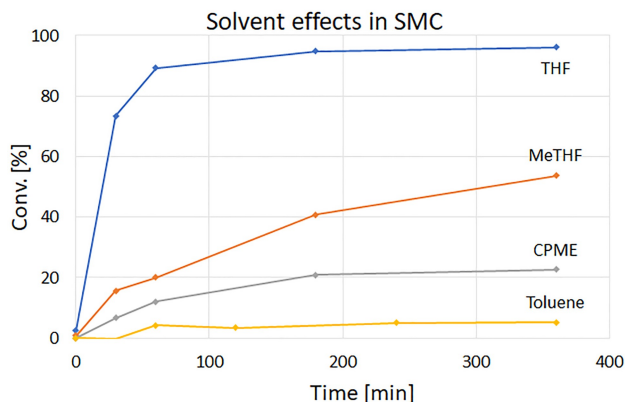
Figure 1. Conversions of 2-bromonaphthalene **2** with 5 mol-% Pd/C, 1.5 equiv. of NaOH, 50 ml of solvent/H$_2$O 1:1 at T_{bp}, using THF (blue), MeTHF (orange), CPME (grey), and toluene (yellow).

less homocoupling product from phenylboronic acid (0.3% of 1,1′-biphenyl **4**). As the main goal of the investigation was to have an efficient and robust catalysis the maximum boiling temperature was investigated for each solvent mixture. Interestingly, a higher temperature did not improve the conversion. For example, the highest temperature used for the reaction in toluene/water (93 °C) showed the worst result in terms of conversion and selectivity. The effective concentration of the oxidative addition reagent, the mass transfer between phases and the effective concentration of available palladium in the reaction media[28] influence the kinetics of reactions catalyzed by heterogeneous catalyst. The viscosity of the solvent is therefore a crucial parameter.[23] Indeed, in our study THF is the best solvent, because it has the lowest dynamic viscosity with about 0.46 mPa*s at 25 °C. Moreover, it has the highest water solubility (33%) with a basic solution at 25 °C.

The water/solvent ratio also influenced the performance of the reaction. Indeed, the increase of THF until a ratio 3:1 THF/water, (maintaining the same concentration of reagents), slowed down the reaction, which is probably due to the greater dilution of the base (mainly for the transmetalation step) and less concentrated reagents in the organic phase during the oxidative addition step. On the other hand, increasing the aqueous phase until a ratio of 2:3 THF/water allowed obtaining almost quantitative conversion and excellent isolated yield (90.8%). Nevertheless, poorer purity (94.5%) due to less selectivity (3.7% of 1,1′-biphenyl **4** as major side-product) was also observed (*Table 3*).

As the solvent is the largest inventory in a reaction, a small quantity of solvent contaminants can have a tremendous impact on catalytic cycle. For this reason, we checked the effect of the contaminants issued from the synthesis route of the following solvents: THF, 2-MeTHF and CPME. High quality solvents are normally used in the pharmaceutical industry. Their quality normally has purities greater than 99.0–99.5%. International cGMP guidelines (ICH) indicate that the identification, control and/or qualification of all impurities greater than 0.10% (1000 ppm) present in an API should be conducted. The same approach is often applied for solvents used in cGMP steps, leading to the use of solvents with purities often greater than 99.8%. Analyses of 'technical' solvents for pharmaceutical industry show only traces of unknown impurities at levels below 500 ppm (*e.g.* industrial-grade CPME contains 80–150 ppm cyclopentanol; THF contains ≤500 ppm 2,3-dihydrofuran (2,3-DHF)). Additionally, industrial THF and 2-MeTHF contains ≈250 ppm of BHT (2,6-bis-*tert*-butylphenol) as stabilizer. No differences in reaction reactivity on Pd/C catalyzed *Suzuki-Miyaura* cross-coupling were noted using THF with or without BHT. On the other hand, approx. 3000 ppm of

Table 3. Synthesis of 2-phenylnaphtalene **3** using different solvents with 5 mol-% Pd/C, 1.5 equiv. of NaOH, solvent/H$_2$O at T_{bp}, under inert atmosphere, end of reaction at six hours. Dynamic viscosity ('Visc') at 298.15 K in mPa*s;[36] Solubility (Sol) of solvent in water at 23 °C in g/100 g.[35,36] Reaction total volume kept constant with different solvent ratio.

Solv	T [°C]	Visc	Sol	Ratio Solv/H$_2$O	Conv. [%]	**3** [%a]	**4** [%a]	Yield of **3** [%]
THF	64	0.46	∞	1:1	97.5	96.2	0.3	83.8
THF	64	0.46	∞	3:1	44.6	76.7	6.4	61.7[a]
THF	64	0.46	∞	2:3	99.9	94.5	3.7	90.8
MeTHF	83	0.48	14	1:1	53.4	39.6	1.5	37.4
CPME	76	0.55[b]	1.1	1:1	22.8	16.3	1.1	16.9
Toluene	93	0.55	5.3	1:1	10.9	13.9	4.4	14.6

[a] The lack of water did not allow for effective removal of excess of base during work-up, overestimating the yield. [b] Dynamic viscosity ('Visc') at 293.15 K.[39]

a precursor like 2,3-DHF in the organic solvent of the studied SMC corresponds to having a 2:1 molar ratio between the contaminant and the Pd catalyst. Therefore, 100–3000 ppm of the impurities reported in the *Figure 2* were investigated, considering the industrial syntheses of THF, 2-MeTHF and CPME.

Initially, almost 2500–3000 ppm (*w/w*) of chosen precursors were spiked to the organic solvent, to obtain a 2:1 molar ratio between the contaminant and Pd.

For the SMC of 2-bromonaphthalene **1** with phenylboronic acid **2** in CPME, the addition of ≈3000 ppm of cyclopentanol increased slightly the final conversion of
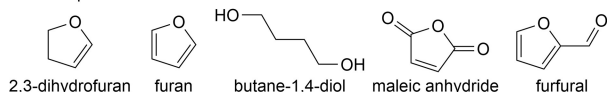
the reaction, but less selectivity was observed (*Table 4*). Cyclopentene and 1,4-butanediol did not change the conversion after 6 h. However, for cyclopentene, a decrease in the purity of the isolated product were observed, indicating that cyclopentene inhibits the catalyst and favors the formation of side-products other than **4**.

For the reaction carried out in THF, the addition of ≈3000 ppm of each precursor/contaminant to the reaction solvent led to a significant decrease of the reaction rate (*Figure 3*). Furfural, furan and 1,4-butanediol seemed to slightly poison the catalyst and the conversion after 6 h decreased by about 15–20%. For the reaction with 1,4-butanediol in THF, unlike in CPME, there is no increase in the formation of the homocoupling product, probably because the reaction rate of the cross-coupling is faster in THF. Indeed, the final conversion as well as the yield decreased in the same proportion without influencing the selectivity of the reaction. On the other hand, 2,3-dihydrofuran and maleic anhydride almost completely stopped the reaction which reached only ≈15% conversion after 6 h of reaction under reflux (*Table 4* and *Figure 3*).
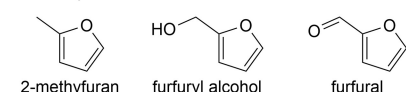
Additionally, all the contaminants of 2-methyltetrahydrofuran (2-methylfuran, furfuryl alcohol and furfural) also poisoned the catalyst and decreased the conversion by ~10%, and even by 20% in the case of furfural. Additionally, ≈3000 ppm of furfural in 2-MeTHF favored the homocoupling by-product **4** at the expense of the quality of the isolated product **3**.

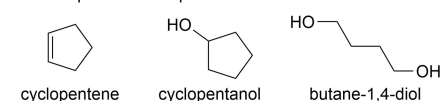**Precursors/impurities from the production of industrial solvents**

Figure 2. Most likely precursor/impurities for the solvents used in SMC.

Table 4. Synthesis of 2-phenylnaphtalene using with 5 mol-% Pd/C, 1.5 equiv. of NaOH, solvent/H_2O, at T_{bp}, under inert atmosphere, 10 mol-% of contaminant. End of reaction after 6 hours.[a]

Contaminant (cont)	Solv	Ratio cont/Pd	Conv. of **1** [%]	**3** [%a]	**4** [%a]	Yield of **3** [%]
–	CPME	–	22.8	16.3	1.1	16.9
Cyclopentanol	CPME	2.0	34.4	17.5	0.9	20.0
1,4-Butanediol	CPME	2.0	20.8	8.0	1.2	9.0
Cyclopentene	CPME	2.1	22.9	4.8	0.4	5.2
–	THF	–	97.5	96.2	0.3	83.8
2,3-Dihydrofuran	THF	2.0	17.9	17.5	0.6	19.9
Furan	THF	2.0	80.8	73.2	0.4	67.9
Furfural	THF	2.0	77.2	77.3	0.7	73.5
1,4-Butanediol	THF	2.0	72.8	59.2	0.7	57.3
Maleic anhydride	THF	2.0	13.9	23.6	0.6	21.6
–	MeTHF	–	53.4	39.6	1.5	37.4
2-Methylfuran	MeTHF	2.0	40.2	18.9	1.1	18.3
Furfuryl alcohol	MeTHF	2.0	40.4	21.8	0.9	23.3
Furfural	MeTHF	2.0	29.3	15.7	1.2	17.0

[a] All the results are the mean of three trials. The conversion is calculated with the ratio between the concentration of the limiting reagent at time 6 h and time t_0. The 2-phenylnaphthalene **3** and biphenyl purity **4** is determined by HPLC (%a = %area). The yield is calculated based on the effective amount of the isolated products, corrected by HPLC purity.
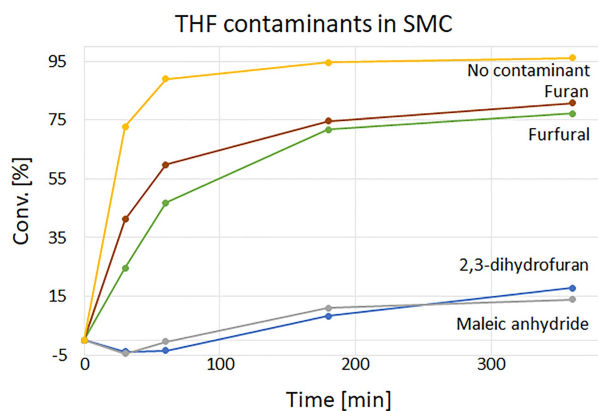
Figure 3. Conversion of 2-bromonaphthalene **1** spiking possible precursors of THF as contaminant. Ratio solvent contaminant/ Pd = 2.0: (5 mol-% Pd/C, 10 mol-% contaminant), 1.5 equiv. of NaOH, 100 ml of THF/H$_2$O 1:1, at 64 °C.
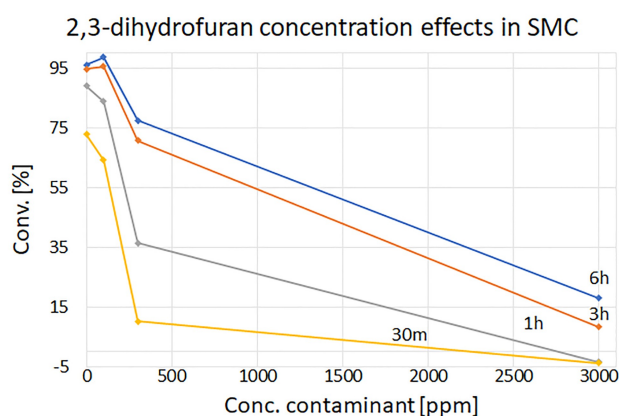

Figure 4. Conversions of 2-bromonaphthalene **1** with 5 mol-% Pd/C, 1.5 equiv. of NaOH, 50 ml of THF/H$_2$O, at 64 °C, using an addition of 3000, 300, 100 and 0 ppm of 2,3-dihydrofuran in THF; after 30 minutes (yellow), one hour (grey), three hours (orange) and six hours (blue).

This poisoning effect was deeply investigated with THF, reducing the quantity of 2,3-dihydrofuran and maleic anhydride up to ≈50–100 ppm (which corresponds to a ratio contaminant/Pd of 0.1): at this level no more poisoning was observed, although the reaction rate was slower the first hour (*Figure 4* and *Table 5*). Increasing the contaminant up to ≈300 ppm (ratio contaminant/Pd of 0.2) a significant decrease of the conversion was observed, indicating that also small traces of this precursor can affect the reaction rate of Pd/C catalyzed *Suzuki-Miyaura* cross-coupling reactions.

As a result, only ≈300 ppm (0.03% w/w) of 2,3-dihydrofurane (which is common in technical solvents in the range 50–500 ppm) in THF had a significant effect on the conversion, which after six hours did not reach completion. Same effect was observed also with ≈300 ppm of maleic anhydride (but this contaminant was never observed above the limit of detection (LoD) in industrial solvents). In order to anticipate possible problems and process deviations (especially when processes are done according to cGMP) a quality control of the solvent should be performed at ppm range for these possible contaminants. Indeed, they have clearly shown to poison the *Suzuki-Miyaura* cross-coupling reaction catalyzed by Pd/C.

To see if our observations are also applicable to other substrates, 12 aryl halides and three boronic acids were tested with the optimized reactions conditions described above (*Figure 5*). These molecules can be the precursors of various end products. Polycycles such as naphthalene derivatives are frequently used in pharmaceutical processes. Performing the SMC with three different boronic acids gave similar results. This was expected because transmetalation is not the kinetically limiting step for the reaction. The reaction also showed good robustness when different aryl

Table 5. Synthesis of 2-phenylnaphtalene **3** with 5 mol-% Pd/C, 1.5 equiv. of NaOH, THF/H$_2$O, at 64 °C, under inert atmosphere, with a spiking of 3000, 300 and 100 ppm of 2,3-dihydrofuran and maleic anhydride, end of reaction after six hours.[a]

Contaminant	Ratio cont/Pd	Conv. of **1** [%]	**3** [%a]	**4** [%a]	Yield of **3** [%]
–	–	97.5	96.2	0.3	83.8
2,3-Dihydrofuran	2.0	17.9	17.5	0.6	19.9
2,3-Dihydrofuran	0.2	77.4	84.6	0.6	65.3
2,3-Dihydrofuran	0.1	98.7	97.3	0.5	85.1
Maleic anhydride	2.0	13.9	23.6	0.6	21.6
Maleic anhydride	0.2	79.9	80.9	0.6	72.4
Maleic anhydride	0.1	95.1	97.2	0.1	81.7

[a] All the results are the mean of three trials. The conversion is calculated with the ratio between the concentration of the limiting reagent at time 6 h and time t_0. The 2-phenylnaphthalene **3** and biphenyl purity **4** is determined by HPLC (%a = %area). The yield is calculated based on the effective amount of the isolated products, corrected by HPLC purity.
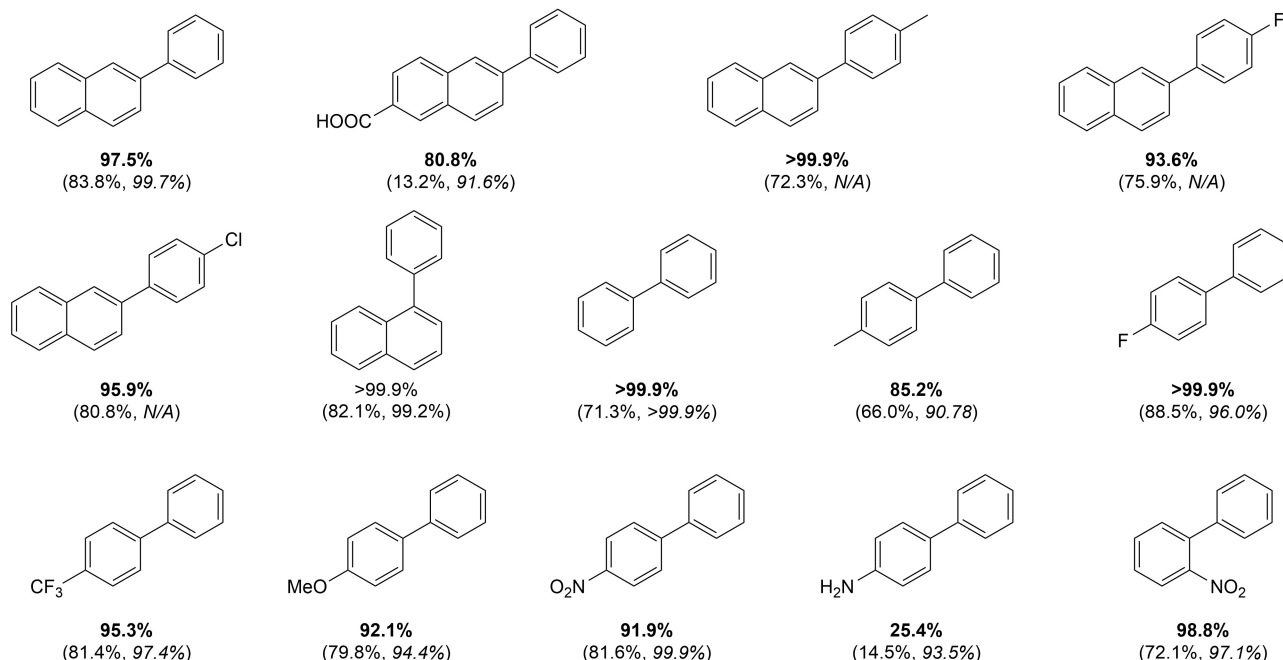
Figure 5. SMC using with 5 mol-% Pd/C, 1.5 equiv. of NaOH, THF/H$_2$O 1:1, at 64 °C, under inert atmosphere, end of reaction (**conversion** of Br-aryl) after six hours. In brackets: yield (normal text) and *selectivity (italic)*.

halides are used. After six hours, conversions of more than 90%, selectivities greater than 95% and yields greater than 70% are observed except for few substrates. The steric hindrance does not seem to influence the reaction as the reaction done with 1-bromonaphthalene or 2-bromonaphthalene or even bromobenzene and 2-nitrobromobenzene gave very high conversion.

A conversion decrease was observed with 4-bromotoluene and 6-bromonaphthoic acid. For the first one, the achieved conversion after 6 h was only 85.2%. The reaction was slower and more homocoupling by-product was formed. For the second one, the achieved conversion was only 80.8%. This low conversion may be due to the acid–base reaction between the substrate and the base (NaOH), which reduces the efficiency of the transmetalation step. 4-Bromoaniline showed poor conversion (25.4%) and poor yield (14.5%). Chlorides are bad halides for SMC and using 2-chloronitrobenzene showed no conversion unlike the 2-bromonitrobenzene that had a 98.8% conversion. Lower yield of isolated products for naphthoic acid and aniline derivatives was related to the simple work-up procedure (removal of catalyst by filtration, separation of aqueous phase, and evaporation of the solvent), which in excess of base led to the loss of a part of the product dissolved in aqueous phase.

Finally, the effect of the contaminants that showed the most important effect on the SMC reaction were further studied with two halides with different electronic properties. For this purpose, only the contaminants 2,3-dihydrofuran and maleic anhydride were chosen.

The halides 4-bromoanisole and 4-bromobenzotrifluoride were selected because the first has an inductive donor effect and the second an inductive withdrawing effect. Both showed excellent conversion in THF without contaminants (*Table 6*). The addition of ≈300 ppm of 2,3-dihydrofuran or ≈300 ppm of maleic anhydride (0.2 ratio contaminant/Pd) showed a more pronounced effect using 4-bromoanisole as starting material, which led also to the formation of more 1,1′-biphenyl **4**. On the other hand, smaller decrease in the reaction rate was noted contaminating the solvent of the reaction of 4-bromobenzotrifluoride with phenylboronic acid catalyzed by Pd/C, with larger effect adding as contaminant maleic anhydride.

To understand better the role of the contaminants, a 'competitive' addition of triphenylphosphine, which is used normally to increase the activity of Pd/C catalysts,[38,39] was investigated. The addition of 0.1 equivalents of triphenylphosphine (ratio 2:1 rela-

Table 6. SMC using 4-bromoanisole (R=OMe) and 1-bromo-4-(trifluoromethyl)benzene (R=CF$_3$) as halide with 0.05 equiv. Pd/C, 1.5 equiv. of NaOH, THF/H$_2$O, at 64 °C, under inert atmosphere, with a spiking of ≈300 ppm of 2,3-dihydrofuran (2,3-DHF) or ≈300 ppm maleic anhydride (MA). Conversion after six hours.[a]
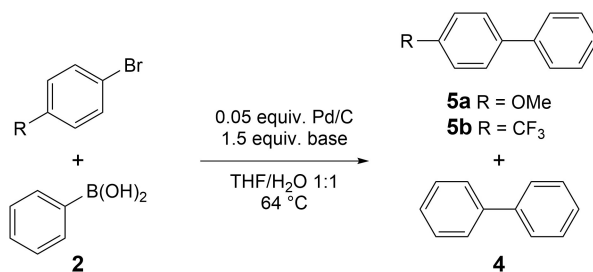
R	Contaminant	PPh$_3$ [equiv.]	Conv. of BrAr [%]	**5a,b** [%a]	**4** [%a]	Yield of **5a,b** [%]
MeO	–	–	92.1	89.9	5.0	79.8
MeO	2,3-DHF	–	69.7	81.5	6.2	64.8
MeO	MA	–	48.8	47.2	10.6	36.0
MeO	2,3-DHF	0.1	98.5	79.6	4.1	71.2
MeO	MA	0.1	96.4	58.6	14.6	56.2
CF$_3$	–	–	95.3	95.5	2.5	81.4
CF$_3$	2,3-DHF	–	93.7	94.2	3.1	76.1
CF$_3$	MA	–	83.2	93.8	4.3	77.6
CF$_3$	2,3-DHF	0.1	97.3	74.7	3.9	73.0
CF$_3$	MA	0.1	92.5	78.7	2.5	79.0

[a] All the results are the mean of at least two trials. The conversion is calculated with the ratio between the concentration of the limiting reagent at time 6 h and time t_0. The 2-phenylbenzene derivatives **5a** and **5b** and biphenyl purity is determined by HPLC (%a=%area). The yield is calculated based on the effective amount of the isolated products, corrected by HPLC purity.

tive to Pd) to a reaction mass contaminated with either 2,3-dihydrofuran or maleic anhydride efficiently prevented the catalyst poisoning and allowed the reaction to achieve similar (or even better) conversion as contaminant-free reactions. Nonetheless, an induction time was observed when triphenylphosphine is used. Most probably, triphenylphosphine coordinates Pd to form the active species. It therefore suggests a homogeneous mechanism,[28] coherent with the higher palladium content found in the isolated product (MP-AES analyses: 6066 ppm of Pd in the isolated product **3** when PPh$_3$ and 2,3-DHF were added; 4–149 ppm of Pd found when no triphenylphosphine was used). Presence of palladium in isolated product indicates that the reaction is probably catalyzed by the solubilized species, as reported by *Köhler et al.* in *Heck* reactions[42] or *Conlon*[28] and *Schmidt*[43,44] in *Suzuki-Miyaura* reactions. Furthermore, the addition of phosphine as ligand is well-known to accelerate the cross-coupling reactions but includes a couple of side-effects for the industrial use: their cost, their removal and increased catalyst leaching. This led the industry searching and using 'phosphine-free' catalysts. On the other hand, in these Pd/C catalyzed reactions, PPh$_3$

helped to solve the inhibition of the catalysts due to the presence of alkene contaminants, able to influence the catalytic activity of palladium. Two scenarios could play a role: either the excess of phosphine increased the rate determining step, by accelerating the oxidative addition (in competition with the alkenes which decreased the oxidative addition rate) or increased the solubility of palladium (and their availability for the catalytic cycle), as suggested by the large Pd-content in the isolated product.

Conclusions

In summary, we have studied the influence of contaminants present in the most used solvents for the biphasic *Suzuki-Miyaura* cross-coupling catalyzed by Pd/C. Our discoveries show that most of the contaminants coming from the precursors of the solvent synthesis lower the conversion, yield and selectivity of the SMC cross-coupling. A 0.2:1 molar ratio of contaminants *versus* Pd is already sufficient to cause a visible effect on the reaction conversion, yield or selectivity. Thus, the control of these contaminants

in solvents should be performed at the ppm level to ensure the robustness of production batches. This is even more important when the amount of catalyst is very low. Adding triphenylphosphine in case of the presence of contaminants help to restore the conversion, yield and selectivity of the cross-coupling reaction. We believe that the present finding will help industries to develop robust processes for Pd/C catalyzed reaction. Most probably, our findings can be extended to other catalytic systems.

Experimental Section

General Methods

All chemicals were purchased from commercial sources (*Sigma Aldrich*, *Alfa Aesar*, *Acros*, *Apollo*) and were used without further purification. The purity of purchased products was confirmed by HPLC analysis. Base line reactions were performed in 100 ml 5-necked glass reactor equipped with a mechanical propeller stirrer, a thermometer, a condenser, a septum and a stopper under an argon/nitrogen atmosphere. The aqueous base and the organic solvent are degassed ultrasonically for 5–15 min and then nitrogen is bubbled for 5–10 min.

Reaction conversion and purity of isolated products were characterized using HPLC (detector: DAD, 230 nm; column: *Phenomenex Kinetex Core-Shell C18* (2.6 μm, 4.6×100 mm); injection: 2 μl; mobile phases: FMA: Water +0.1% HCOOH; FMB MeCN+0.1% HCOOH; flow: 0.8 ml/min; gradient details in the *Supporting Information*. Purity of isolated products and their retention time in HPLC were compared with purchased products, when available.

General Experimental Procedure

Bromoaryl (3.0 g, 1.00 equiv.), arylboronic acid (1.10 equiv.) and 0.05 equiv. of Pd/C (10% of Pd on C, *Noblyst P1067*, 50% wet) were added to 400 ml reactor. The reactor was inertized with three cycles vacuum/N_2. Degassed solvent (50 ml, 16.6 *v/w*) was added by syringe and the reaction mass was stirred at 800 rpm and heated to boiling point. An aqueous solution of base (1.5 equiv. dissolved in 16.6 *v/w* water) was added through a syringe, and the reaction mass was stirred at boiling temperature for at least 6 h. In-process-control samples (t_0, 30 min, 60 min, 180 min and 360 min) were analyzed after 0.45 μm filtration. The reaction mass was cooled to room temperature,

filtered through a 0.45 μm membrane. The biphasic system was separated, and the organic phase was evaporated to dryness (rotary evaporator, <10 mbar, 40–45°C, overnight). Isolated products were analyzed as is, without further purifications. Yield referred to the amount of isolated solid, corrected by HPLC purity.

Example 1: Synthesis of 2-Phenylnaphthalene in THF

2-Bromonaphthalene **1** (3.03 g, 14.1 mmol, 1.00 equiv.), phenylboronic acid **2** (2.02 g, 95% purity, 15.5 mmol, 1.1 equiv.) and Pd/C (1.52 g, 0.7 mmol, 10% of Pd on C, *Noblyst P1067*, 50% wet) were added to a 400 ml reactor. The reactor was inertized with three cycles vacuum/N_2. Degassed THF (44.4 g, 16.6 *v/w*) was added to the reactor and the reaction mass was stirred at 800 rpm and heated at 64°C (internal temperature). A degassed aqueous solution of NaOH (0.86 g, 98% assay, 21 mmol, 1.5 equiv.) dissolved in water (50 g, 16.6 *v/w*) was added through a syringe, and the reaction mass was stirred at boiling temperature for 6 h. In-process-control samples (t_0, 30 min, 60 min, 180 min and 360 min) were taken for analysis (after 0.45 μm filtration). The reaction mass was cooled to room temperature, filtered through a 0.45 μm membrane. The biphasic system was separated, and the organic phase was evaporated to dryness (rotary evaporator, <10 mbar, 40–45°C, overnight), affording 2.62 g of yellowish solid (89.1% yield, corrected by HPLC purity). ^{1}H-NMR (400 MHz, CDCl$_3$): 8.08 (*d*, *J*=1.9, 1H); 7.98–7.85 (*m*, 3H); 7.80–7.75 (*m*, 3H); 7.59–7.46 (*m*, 4H); 7.46–7.36 (*m*, 1H). HPLC Purity (a%): 98.06% (related substances: 0.21% Phenylboronic acid **2**, 0.19% RRT0.81, 0.24% 1,1'-biphenyl **4**, 1.30% 2-bromonaphthalene **1**).

Example 2: Synthesis of 2-Phenylnaphthalene Adding 225 ppm of 2,3-Dihydrofuran as THF Contaminant (ratio contaminant/Pd=1:5)

2-Bromonaphthalene **1** (3.01 g, 14.1 mmol, 1.00 equiv.), phenylboronic acid **2** (1.99 g, 95% purity, 15.5 mmol, 1.1 equiv.) and Pd/C (1.51 g, 0.7 mmol, 10% of Pd on C, *Noblyst P1067*, 50% wet) were added to a 400 ml reactor. The reactor was inertized with three cycles vacuum/N_2. Degassed THF (44.4 g, 16.6 *v/w*) containing 225 ppm of 2,3-dihydrofuran (10 mg, 0.14 mmol) was added to the reactor, and the reaction mass was stirred at 800 rpm and heated ta 64°C (internal temperature). A degassed aqueous solution of NaOH (0.86 g, 21 mmol, 1.5 equiv.) dissolved in water (50 g, 16.6 *v/w*) was added, and the reaction mass was stirred at 64°C for 6 h. In-process-control samples (t_0, 30 min, 60 min, 180 min and 360 min) were taken for analysis (after 0.45 μm filtration).

Acknowledgements

Author Contribution Statement

The manuscript was written through contribution of all authors. All authors have given approval to the final version of the manuscript. The authors declare no competing financial interest.

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