

# Suzuki–Miyaura Cross-Coupling With Quasi-Heterogeneous Palladium

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**Abstract:** The Suzuki–Miyaura cross-coupling reaction using heterogeneous Pd/C has a homogeneous component. The soluble palladium concentration increases during the reaction reaching a maximum at *ca.* 90% conversion before falling to < 4 ppm.

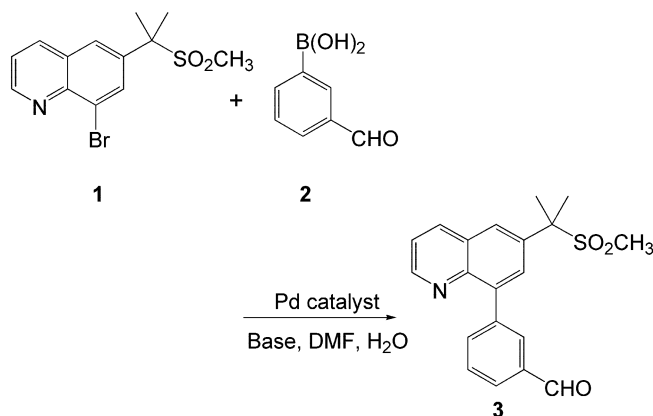
**Keywords:** cross-coupling; heterogeneous catalyst; palladium; palladium leaching; Suzuki–Miyaura

Suzuki–Miyaura cross-coupling has proven to be an excellent procedure for the convergent syntheses of pharmaceutical intermediates and fine chemicals due to the relatively mild reaction conditions which can tolerate a variety of functional groups.<sup>[1]</sup> The Suzuki–Miyaura cross-coupling reaction of arylboronic acids and aryl halides is catalyzed by a variety of different metal complexes and is an effective means of producing biaryls.<sup>[1,2]</sup> Especially for pharmaceutical synthesis, the choice of the catalyst and its impact on reaction time and yield are often not the only considerations for choosing a viable synthetic procedure. Of paramount concern are the simplicity of product isolation and the presence of residual organic and inorganic impurities. While homogeneous catalysts are typically utilized, there has been increasing interest in heterogeneous catalysts because their use greatly simplifies product isolation and often reduces organic and inorganic impurities. In this paper, we show that the heterogeneous catalyst Pd/C is an excellent catalyst for the preparation of the advanced key intermediate **3** in the synthesis of an investigational drug candidate and we provide insight into the behavior of the catalyst during the reaction.

The palladium-catalyzed Suzuki–Miyaura cross-coupling reaction between the bromoquinoline **1** and the commercially available 3-formylphenylboronic acid **2** was a logical option for the preparation of aldehyde **3**.

A variety of different metal complexes have been reported as catalysts for the Suzuki–Miyaura reaction.<sup>[1,2]</sup> An initial screening of several homogeneous palladium catalysts identified Pd(dppf)Cl<sub>2</sub> as an excellent catalyst for this coupling.<sup>[3]</sup> Unfortunately, the isolated aldehyde **3** contained high levels of residual palladium, as well as, iron<sup>[4]</sup> from the dppf ligand. Reduction of the residual Pd concentration and removal of the dppf ligand to acceptable levels represented a major challenge for the production of **3** of suitable quality.

Phosphine ligands are effective in stabilizing Pd(0) species; however, Novak and Wallow reported that using phosphine-free palladium precursors accelerated the Suzuki–Miyaura cross-coupling reaction.<sup>[5]</sup> Several other reports have described the successful application of ligandless systems including palladium nanoparticles.<sup>[6]</sup> Nonetheless, separation of the residual palladium from **3** would still be an issue for many of these procedures. In order to avoid additional processing steps and associated yield loss, we investigated the use of ligandless, heterogeneous Pd/C as the catalyst for this cross-coupling.<sup>[7]</sup> The use of Pd/C has several advantages including significant cost reduction, availability of



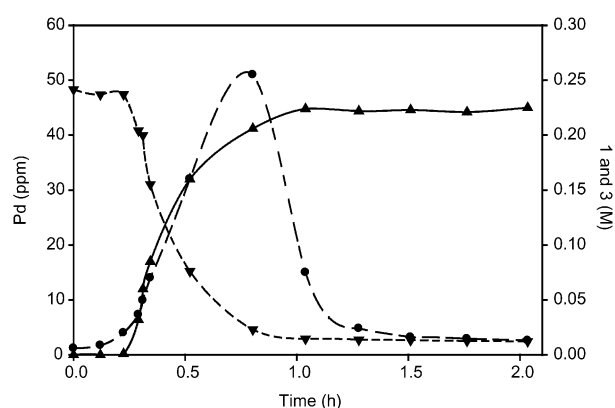
**Scheme 1.** Suzuki–Miyaura cross-coupling reaction.

several different compositions, facile removal by filtration and most importantly, Pd/C has been successfully used as a catalyst for the Suzuki–Miyaura cross-coupling in large-scale syntheses of biaryl compounds.<sup>[8]</sup> Ennis et al. reported that a coupling reaction with the soluble palladium catalyst Pd(PPh<sub>3</sub>)<sub>4</sub> gave residual Pd levels of 40–80 ppm and by switching to Pd/C the level was reduced to < 6 ppm.<sup>[8c]</sup> An added advantage of Pd/C is that it does not require added ligand that could potentially become a contaminant or produce unwanted coupling products due to transfer of an aryl group from the phosphine ligand to the palladium.<sup>[9]</sup>

After screening a variety of supported palladium catalysts,<sup>[10]</sup> we determined that the optimum catalyst for the reaction to form **3** had non-reduced palladium distributed on the activated carbon surface (an egg-shell dispersion). Both dry catalyst and water-wet catalyst performed equally well in the reaction.<sup>[11]</sup> Optimization of the Pd level (2.6 mol %) and the reaction conditions (DMF:water/10:1, K<sub>2</sub>CO<sub>3</sub>, 80 °C) resulted in reproducible isolated yields of aldehyde **3** of 85–92% with residual Pd levels between 18–80 ppm. Further processing of **3** to the final target resulted in a reduction of the palladium level to < 10 ppm.

The potassium carbonate in this system produces hydroxide ion, which in turn generates the tetrahedral boronate anion necessary for the transmetalation step. Fluoride ion has been shown to be an acceptable replacement for hydroxide ion.<sup>[12]</sup> Substituting potassium fluoride for potassium carbonate during formation of **3** resulted in similar yields. However, significant variation of the palladium levels in isolated **3** was observed, ranging from 90 to 3180 ppm. Although early reports<sup>[8a]</sup> provide strong evidence that the Pd/C cross-coupling reactions are heterogeneous, the palladium levels with KF as the base approach those observed with the homogeneous catalyst, Pd(dppf)Cl<sub>2</sub>. In addition, extensive debate regarding whether reactions with heterogeneous Pd/C catalyst are truly heterogeneous or simply a source of soluble palladium exists. Several recent reports have challenged a strictly heterogeneous reaction mechanism when Pd/C is used as a catalyst.<sup>[5,13]</sup> These reports detail substantial leaching of the palladium from the surface and a quasi-heterogeneous catalyst system.

The higher levels of palladium and the wide variation in the residual palladium level prompted further investigation into the soluble palladium concentration in the reaction mixture as a function of time. In order to gain a better understanding of the reaction process we decide to focus on this system in detail. Reaction samples were analyzed following filtration through a 0.45 µm filter for the concentration of **1**, **2**, **3**, and palladium.<sup>[14]</sup> The results, presented in Figure 1, show that the concentration of soluble palladium increased as the reaction proceeded reaching a maximum when the percent conversion was *ca.* 90, and then decreased with time.<sup>[15]</sup>



**Figure 1.** Plot of concentrations of **1** (▼), **3** (▲), and palladium (●) as a function of time (See Table 1, Entry 2).

The above findings motivated considerable thought into the underlying physical and chemical mechanisms controlling the formation of **3** in the heterogeneous system. Analysis for soluble palladium in a mixture of Pd/C and DMF at 80 °C confirmed the absence of palladium leaching. Thus, there is initially little or no soluble Pd in the reaction mixture suggesting that palladium desorption occurs as a result of the reaction conditions (temperature/reagents) and/or the reaction itself. Biffis observed during the study of supported palladium catalysts in the Heck reaction that palladium leaching occurred only in the presence of an aryl halide.<sup>[16]</sup> Therefore, it is assumed that desorption of palladium from the carbon surface occurs after the oxidative addition of **1** on the surface of the palladium and generates a soluble Pd(II) species. However, the non-ligand-stabilized Pd(II) complex [PhPdBr] prepared by the cocondensation of palladium atoms with bromobenzene was reported to be unstable above –116 °C.<sup>[17]</sup> It is also important to note that ligandless zero-valent palladium is not known to exist in solution as a molecular species.<sup>[18]</sup> It is unclear at this time, in what form or structure the soluble palladium exists. A key observation was that the decay of the solution phase palladium shown in Figure 1 coincides with nearly complete consumption of the bromoquinoline **1**. This suggested that the oxidative addition step was responsible for the desorption of the palladium from the carbon and that the consumption of **1** slowed the rate of desorption.<sup>[19]</sup>

To further investigate the oxidative addition as the leaching mechanism, various carbon supports and Pd loadings were studied. The maximum Pd concentration and time to achieve the maximum for several catalysts are shown in Table 1. Entries 1 and 2 compare two 5% Pd/C catalysts on different carbon supports. The maximum level of palladium differs by a factor of two, indicating the affect of the type of carbon support on the soluble palladium levels. Entries 2 and 3 compare 5% and 10% catalysts on the same carbon support. The 10%

**Table 1.** Suzuki–Miyaura cross-coupling reactions with Pd/C.<sup>[a]</sup>

| Entry            | Catalyst             | Base                           | Initial relative rates <sup>[b]</sup> | Time [h] to reach maximum Pd | Maximum Pd level in solution [ppm] <sup>[c]</sup> | Time [h] to reach $\leq 4$ ppm |
|------------------|----------------------|--------------------------------|---------------------------------------|------------------------------|---------------------------------------------------|--------------------------------|
| 1                | 5% <sup>[d]</sup>    | K <sub>2</sub> CO <sub>3</sub> | 1.15                                  | 1.4                          | 102                                               | 3.3                            |
| 2                | 5% <sup>[e]</sup>    | K <sub>2</sub> CO <sub>3</sub> | 1.23                                  | 0.8                          | 51                                                | 1.5                            |
| 3                | 10% <sup>[f]</sup>   | K <sub>2</sub> CO <sub>3</sub> | 1.75                                  | 0.6                          | 103                                               | 2.0                            |
| 4                | 10% <sup>[f,g]</sup> | K <sub>2</sub> CO <sub>3</sub> | 1.42                                  | 0.6                          | 61                                                | 1.6                            |
| 5                | 10% <sup>[f]</sup>   | KF                             | 1.00                                  | 1.8                          | 273                                               | > 4.4                          |
| 6 <sup>[h]</sup> | 10% <sup>[f]</sup>   | KF                             | 4.44                                  | 0.08                         | 178                                               | 3.6                            |

<sup>[a]</sup> All reactions were performed with 0.11 mol **1**, 0.16 mol of **2**, and 2.6 mol % palladium.

<sup>[b]</sup> The initial rates were determined for the change in [**3**] after the reaction reached 80 °C.

<sup>[c]</sup> Solutions were digested in concentrated HNO<sub>3</sub> and diluted 1 : 1 with de-ionized water. Pd analysis was performed by ICP-MS.

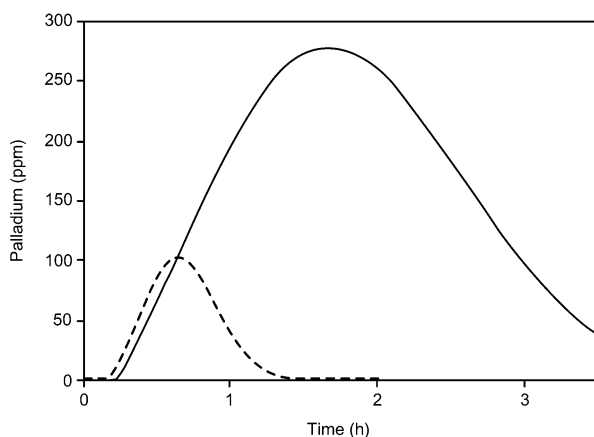
<sup>[d]</sup> Englehard C6064 catalyst.

<sup>[e]</sup> Johnson Matthey A405023–5 catalyst.

<sup>[f]</sup> Johnson Matthey A402032–10 catalyst.

<sup>[g]</sup> Added Johnson Matthey Carbon Support #032.

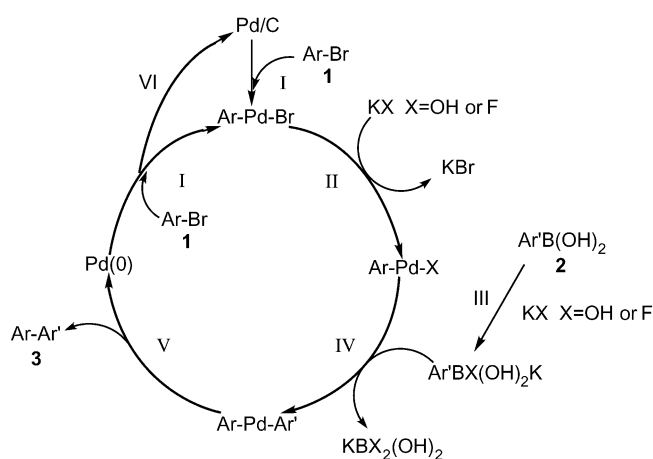
<sup>[h]</sup> With 0.32 mol of **2** (double the typical concentration).



**Figure 2.** Palladium concentration as a function of time for the Suzuki–Miyaura cross-coupling with K<sub>2</sub>CO<sub>3</sub> (– –) and KF (—), see Table 1 Entries 3 and 5, respectively

Pd/C catalyst has half the amount of carbon support and generates twice the amount of soluble palladium, suggesting a correlation between the amount of carbon support and the level of soluble Pd. This assertion is further supported by Entry 4 where carbon support was added to the 10% Pd/C catalyst to achieve a carbon loading equivalent to the 5% Pd/C catalyst. In this case, the maximum soluble palladium concentration (61 ppm) is comparable to that observed with 5% Pd/C (Entry 2, 51 ppm). These findings demonstrate the correlation between the carbon support and the concentration of soluble Pd and also support a facilitated-desorption mechanism controlled by the oxidative addition of bromoquinoline **1**.

The overall shape of the curve in Figure 1 with Pd concentration increasing as a function of time (or conversion of **1**) also suggests that oxidative addition is not the rate-determining step for this reaction. Support for this hypothesis is shown in Figure 2 where two cross-



**Figure 3.** Proposed catalytic cycle for the Pd/C-catalyzed Suzuki–Miyaura cross-coupling.

I: Oxidative addition; II: Halide metathesis; III: Formation of tetrahedral intermediate; IV: Transmetalation; V: Reductive elimination; VI: Pd precipitation.

coupling reactions were performed under identical conditions except for the base. The rates for solubilization of palladium are similar for reactions with either K<sub>2</sub>CO<sub>3</sub> or KF. However, the maximum Pd concentration is greater and the time to achieve that maximum is longer for KF, suggesting that a step after the oxidative addition is rate determining. This suggested that variations in residual palladium levels in isolated **3** when KF is the base, are probably due to differences in the amount of time elapsed between determination that the reaction was complete and commencement of the reaction work up.

Three of the steps in the catalytic cycle shown in Figure 3 are potentially affected by the base: the metathesis (II), formation of tetrahedral boronate (III),<sup>[20]</sup> and transmetalation (IV). To further probe the mech-

anism, a reaction with double the initial concentration of **2** was performed with KF as the base (see Table 1, Entry 6). The time to reach the maximum Pd concentration was significantly reduced in this case (compare Entries 5 and 6 in Table 1) suggesting that transmetalation is the rate-limiting step. Thus, the accumulation of soluble Pd is a result of the slow step in the mechanism, and the base contributes to the overall rate through enhancement in the reactivity and/or concentration of the species<sup>[21]</sup> involved in the rate-determining step.

In conclusion, the Pd/C-catalyzed Suzuki–Miyaura reaction was shown to give **3** in excellent yield with low levels of residual palladium after a simple filtration and precipitation. The low level of residual palladium is an important criterion for pharmaceuticals and the use of a heterogeneous catalyst is motivated by the ease of separation of the palladium from the product. In the example above, dissolution of palladium from the carbon support occurred during the oxidative addition step. Observation of soluble palladium is attributed to differences in the relative rates for the oxidative addition step that brings palladium into solution and the rate of precipitation that removes palladium. These rates were shown to be dependent on the base, the amount and type of carbon support and the time elapsed between reaction completion and product isolation. The overall reaction rate does not correlate to the soluble palladium concentration indicating that the rate-determining step is the transmetalation step. The study presented here indicates a homogeneous pathway, whether there is a heterogeneous component to this reaction and the nature of the soluble palladium are issues that still need to be resolved.

## Experimental Section

### Typical Suzuki–Miyaura Reaction Procedure

A 1.2-L temperature-controlled, jacketed reactor vessel (RC1, Mettler-Toledo) equipped with an overhead stirrer (1000 rpm) was charged with 364 mL of DMF and the system was degassed using 3 vacuum/nitrogen back-fills. Bromoquinoline **1** (37.64 g) was charged and the solution was degassed as above. 3-Formylphenylboronic acid (24.07 g) was added and the solution was degassed. The base ( $K_2CO_3$ , 47.54 g or KF 20.7 g) was added and the slurry was degassed. The Pd/C catalyst (2.6 mol %) and 36 mL of water were added and the reaction mixture was degassed and heated to 80 °C at 3 °C/min. Samples were removed during the course of the reaction, filtered hot through a 0.45  $\mu$ m filter, and the filtrates were analyzed by HPLC for organics and ICP-MS for palladium. After HPLC analysis determined that the reaction was complete (<2 LCAP of **1**), the mixture was filtered through a bed of solka floc. A hot DMF flush of the waste cake was combined with the filtrate and **3** was precipitated by the addition of an equal volume of water. After filtration and washing, the tan solid was dried in a vacuum oven to give of **3**; yield: 34.4–37.3 g (85–

92%); mp 182–184 °C;  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  = 2.03 (s, 6H), 2.66 (s, 3H), 7.51 (dd,  $J$  = 4.1, 8.2 Hz, 1H), 7.69 (t,  $J$  = 7.6 Hz, 1H), 7.98 (m, 2H), 8.08 (d,  $J$  = 2.1 Hz, 1H), 8.12 (d,  $J$  = 2.2 Hz, 1H), 8.23 (m, 1H), 8.28 (m, 1H), 9.00 (dd,  $J$  = 1.8, 4.2 Hz, 1H), 10.13 (s, 1H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$  = 22.9, 35.0, 64.7, 122.0, 128.0, 128.3, 128.9, 128.9, 129.9, 132.3, 135.8, 136.4, 136.8, 137.0, 139.7, 140.0, 145.4, 151.6, 192.4; anal. calcd. for  $C_{20}H_{19}NO_3S$ : C 67.97, H 5.42, N 3.96, S 9.07; found: C 67.86, H 5.11, N 3.92, S 8.99.

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