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Palladium on carbon as a precatalyst for the Suzuki–Miyuara cross-coupling of aryl chlorides

Joseph P. Simeone[a,b,*] and John R. Sowa, Jr.[a,*]

[a]*Department of Chemistry and Biochemistry, Seton Hall University, South Orange, NJ 07079, USA*
[b]*Department of Drug Metabolism and Pharmacokinetics, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA*

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Abstract—Palladium on carbon is used as a precatalyst for Suzuki–Miyaura reaction of aryl chlorides and aryl boronic acids. An efficient catalyst system is obtained that allows the reaction of substrates that are difficult to couple under ligand free conditions. This includes electron rich and sterically hindered aryl chlorides as well as electron deficient and sterically hindered boronic acids. We have discovered that the amount of ligand needed to catalyze these reactions can be significantly decreased by incorporating an incubation period. This study also provides valuable insight into the mechanism of the Pd/C-catalyzed Suzuki–Miyaura cross-coupling. For example, mercury poisoning studies provide evidence that the active catalytic species is homogeneous. However, catalyst reuse and low metal contamination indicate that this system retains many of the advantages of a heterogeneous catalyst. From these results, a catalytic cycle is proposed.

1. Introduction

Since its discovery in 1980, Suzuki–Miyaura cross-coupling reaction has been widely used in academic and industrial research laboratories.[1–4] Recently, it has been successfully employed on a manufacturing scale. Our interest in this reaction stems from the desire to develop an efficient procedure that is more economical, environmentally friendly, and results in products with lower metal-based contaminants than one obtains with homogeneous catalysts. Thus, we and others have extensively researched the use of the well known heterogeneous catalyst, palladium on carbon, for this reaction.[5]

Previously, we have evidence suggesting that palladium on carbon works as a quasi-heterogeneous catalyst where the initial solid material leaches a catalytic species that is eventually redeposited on the carbon surface as the reaction nears completion.[6] While we cannot rule out a heterogeneous component to the reaction, there is mounting evidence in the current literature suggesting that there is a dominant homogeneous component to most Pd/C-catalyzed coupling processes.[7,8] Thus, this well known catalyst has been proven by us and others to be a practical catalyst for the coupling of aryl bromides, resulting in high yields and very low palladium contamination.

Aryl chlorides have been a target reaction for Suzuki–Miyaura couplings because they are more atom economical and cheaper than aryl bromides or iodides.[9] In a previous study, we showed that palladium on carbon is also an excellent catalyst for the coupling of aryl chlorides, provided that they contain electron withdrawing groups.[10] Unfortunately, coupling reactions using electron neutral and electron donating aryl chlorides were found to be both low yielding and to contain significant homo-coupling by-products. Thus, we became interested in the challenge of developing a Suzuki–Miyaura reaction using palladium on carbon with aryl chlorides containing electron neutral and donating groups. We were encouraged by the brief reports from Nishida and Tagata (focused on heteroaromatic chlorides)[11] and Joshaghani et al. (focused on palladium acetate)[12] in which they described increased yields for the Pd/C-catalyzed Suzuki–Miyuara coupling when biphenyl based phosphine ligands were added to the reaction mixture. These studies suggested the possibility of broader development of Pd/C-catalyzed coupling of aryl chlorides using ligand assisted Pd/C.

Our efforts have resulted in a high yielding, general coupling reaction of aryl chlorides; including the ability to couple hindered aryl chlorides (Scheme 1). In addition, this method reaps some of the benefits inherent in a heterogeneous catalyst; including ease of separation of the catalyst from the product, and low metal contamination. The palladium leaching process, which is a unique property of an immobilized catalyst, allows for low ligand loadings for some substrates.

Keywords: Aryl chloride; Biaryl; Biphenyl; Cross-coupling; Homogeneous catalyst; Heterogeneous catalyst; Palladium on carbon.
* Corresponding authors. Tel.: +1 732 594 4307; fax: +1 732 594 6921; e-mail: joe_simeone@merck.com

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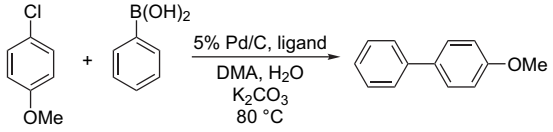
Moreover, we are able to provide valuable insight into the nature of the soluble palladium component of the catalyst.



Scheme 1. Ligand assisted Pd/C-catalyzed Suzuki–Miyuara reaction.

2. Results and discussion

2.1. Optimization studies

Previously, we demonstrated that ligandless Pd/C was effective in the Suzuki–Miyaura coupling of aryl chlorides provided they contain electron withdrawing groups.[10] Attempted coupling of electron donating aryl chlorides such as 4-chloroanisole resulted in low yields (<30%) and low chemoselectivities. However, Nishida and Tagata[11] demonstrated the use of phosphines (PPh_3, 2-(dicyclohexylphosphino)biphenyl) for the Pd/C-catalyzed coupling of heteroaromatic chlorides. In this report there was only one example of an electron donating (non-heteroaromatic) aryl chloride. A report by Joshaghani et al.[12] provided an additional example of a Pd/C-catalyzed coupling of an electron donating aryl chloride in the presence of a biphenyl based phosphine ligand. Thus, these examples suggest the potential for broader development of ligand assisted Pd/C coupling of electron donating aryl chlorides.

A screen of commercially available ligands revealed that triphenylphosphine and bidentate ligands dppf and Xantphos completely inhibited the cross-coupling when as little as 2.5 mol % of ligand relative to aryl chloride was added (Table 1, entries 1–7). Also, in our hands, monodentate biphenyl based ligands at levels similar to those used by Nishida and Tagata[11] (10 mol %, entries 8 and 10) resulted in low conversions. However, reducing the amount of these ligands to an amount equivalent to the palladium loading, 2.5 mol %, resulted in significant and practical increase in product conversions. The most effective ligands were the multisubstituted biphenylphosphines (entries 14–17), giving product conversions as high as 91%.

We also examined the reaction conditions by screening a number of common solvents (ethanol, DME, NMP) at a 20:1 ratio with water in the presence of 2.5 mol % MePhos. We also varied the base (Na_2CO_3, KOAc, NaOH), the mole percentage of palladium (2.5%, 1.25%, 0.125%), and the palladium source (Degussa, PMC, Alfa Aesar, Engelhard), while keeping the palladium type constant (unreduced, 50% water-wet, egg-shell dispersion). No combination of these conditions proved to be superior to the DMA/K_2CO_3 system and the yields were similar for the catalysts obtained from the different vendors.

2.2. Reaction scope

Encouraged by the greater than twofold increase in product conversion in the presence of ligand, we screened additional substrates that were difficult to couple under ligandless conditions. As shown in Table 2, each reaction shows significant increases in yield in the presence of ligand. Even the unfavorable reaction between the electron rich 4-chloroanisole and electron deficient 4-formylphenylboronic acid resulted in a 30% yield (entry 2).

A major advantage of multisubstituted biphenyl based ligands is the ability to catalyze the Suzuki–Miyuara coupling of sterically hindered aryl halides and boronic acids.[13] The MePhos ligand gave only low conversions for hindered reactants. However, as shown in Table 3, XPhos enables the cross-coupling of hindered substrates in good yields (70–91%). The efficiency of this process is highlighted by the coupling of 2-chloro-*m*-xylene and *o*-tolylboronic acid (Table 3, entry 5), which failed to yield any isolable product under ligandless conditions but proceeded in 71% yield with XPhos. Even the pair of substrates that did not work well, 2-chloroanisole and *o*-tolylboronic acid, gave a 30% yield with

Table 1. The effect of ligand on the Pd/C-catalyzed Suzuki–Miyuara cross-coupling of 4-chloroanisole and phenylboronic acid[a]

Entry	Ligand	Mol (%)	Conversion[b] (%)
1	None	n/a	37[c]
2	Triphenylphosphine	10	0
3	Triphenylphosphine	2.5	1
4	dppf[d]	10	0
5	dppf	2.5	3
6	Xantphos[e]	10	0
7	Xantphos	2.5	0
8	2-(Di-*tert*-butylphosphino)biphenyl	10	14
9	2-(Di-*tert*-butylphosphino)biphenyl	2.5	58
10	2-(Dicyclohexylphosphino)biphenyl	10	36
11	2-(Dicyclohexylphosphino)biphenyl	5	47
12	2-(Dicyclohexylphosphino)biphenyl	2.5	56
13	2-(Dicyclohexylphosphino)biphenyl	1	18
14	2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl	2.5	88
15	MePhos[f]	2.5	91
16	MePhos	1.25	71
17	Xphos[g]	2.5	79

[a] All reactions were performed with 0.8 mmol 4-chloroanisole, 0.96 mmol phenylboronic acid, 1.6 mmol K_2CO_3, 0.02 mmol 5% Pd/C, and 0.02 mmol ligand, in 5 mL of 20:1 (v/v) DMA:H_2O at 80 °C for 24 h.
[b] Corrected HPLC conversions are defined as (mmol 4-methoxybiphenyl)/(mmol 4-chloroanisole+mmol 4-methoxybiphenyl)×100.
[c] See Ref. 10.
[d] 1,1′-Bis(diphenylphosphino)ferrocene.
[e] 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene.
[f] 2-Dicyclohexylphosphino-2′-methylbiphenyl.
[g] 2-Dicyclohexylphosphino-2′,4′,6′-trisopropylbiphenyl.

Table 2. Ligand free versus MePhos assisted Pd/C-catalyzed Suzuki–Miyuara cross-couplings of aryl chlorides[a]

Entry	X–C_6H_4Cl	Y–$C_6H_4B(OH)_2$	Ligand assisted yield[b] (%)	Ligand free yield[b] (%)
1	4-OCH_3	H	66	32[c]
2	4-OCH_3	4-CHO	30	0
3	4-CH_3	H	61	36[c]
4	H	4-CHO	80	8
5	4-CH_3	2-F	71	27

[a] All reactions were performed with 0.8 mmol 4-chloroanisole, 0.96 mmol phenylboronic acid, 1.6 mmol K_2CO_3, 0.02 mmol 5% Pd/C, and 0.02 mmol MePhos, in 5 mL of 20:1 (v/v) DMA:H_2O at 80 °C for 24 h.
[b] Isolated yield.
[c] See Ref. 10.

Table 3. Ligand free versus XPhos assisted Pd/C-catalyzed Suzuki–Miyuara cross-couplings of aryl chlorides[a]

Entry	X–C_6H_4Cl	Y–$C_6H_4B(OH)_2$	Ligand assisted yield[b] (%)	Ligand free yield[b] (%)
1	4-CH_3	2-CH_3	91	27
2	2-CH_3	H	71	15
3	2-CH_3	2-CH_3	80	7
4	2-OCH_3	2-CH_3	30	0
5	2,6-Dimethyl	2-CH_3	71	0
6	2-CH_3	4-CHO	86	n.d.
7	2,6-Dimethyl	2-F	70	n.d.
8	4-OCH_3	2-F	75	n.d.

[a] All reactions were performed with 0.8 mmol 4-chloroanisole, 0.96 mmol phenylboronic acid, 1.6 mmol K_2CO_3, 0.02 mmol 5% Pd/C, and 0.02 mmol XPhos, in 5 mL of 20:1 (v/v) DMA:H_2O at 80 °C for 24 h.
[b] Isolated yield.

XPhos; however, no product was obtained in the ligandless reaction. In terms of product yield, we find XPhos assisted reactions for these hindered systems are comparable[13] or superior[14] to those reported for homogeneous precatalysts.

2.3. Low ligand loading experiments

Initial studies at low phosphine loading gave poor results when less than 2.5 mol % was employed. However, from our previous work on ligandless Pd/C systems we were aware that extremely low levels of soluble palladium are present throughout the time course of the reaction and that soluble palladium levels increase throughout the reaction, only as long as aryl halide is present.[6] Also, from this and earlier studies, we had evidence that high ligand loading is detrimental to the reaction, perhaps due to overcoordination of the ligand to the metal.[15] We reasoned that at the onset of the reaction, when soluble palladium levels are low, the ligand concentration may be high enough to inhibit some reactions. One way to overcome this problem would be to delay the addition of the ligand until the soluble palladium concentration increases.

Thus, we designed experiments whereby low levels of ligand (0.3 mol %) are added to the reaction mixture after a short incubation period. Initially, we experienced difficulty adding the ligands because they were insoluble in dimethylacetamide. However, solid addition proved to be effective when using a positive counter current of argon. As seen in Table 4, this protocol allows coupling reactions at low ligand loadings. The reaction between 4-chloroanisole and phenylboronic acid (entries 1–3) is equally effective at a ligand loading of 0.3 mol % (63% yield, 24 h) as at 2.5 mol % (66% yield, 24 h, Table 2, entry 1) provided an incubation time of 3 h at 80 °C is used. Without incubation, the yield is similar to the ligandless reaction. Even more remarkable are the results for the coupling between 2-chlorotoluene and phenylboronic acid (entries 4–8). Incorporating an incubation time of either 3 h at 80 °C or 15 min at 100 °C results in a fourfold increase in product yield (90%) versus reaction without an incubation period (~20% yield).

Coupling of heteroaromatic compounds is desirable. Thus, we successfully prepared 3-(2-methylphenyl)pyridine (entries 9–11) in a yield of 53% after 23 h at 100 °C. In contrast, previously this compound has been prepared[13] with more than ten times the ligand loading using a homogeneous precatalyst ($PdOAc_2$). However, this reaction does not appear to require an incubation period. Remarkably, the ligandless reaction failed to yield any product, instead only unreacted 2-chlorotoluene was observed by HPLC. Protodeboronation of the 3-pyridylboronic acid occurred in all reaction studies and likely limited the overall yield of this reaction. Also, the cross-coupling of 4-chloroanisole with 2,4-difluorophenylboronic acid (entries 12–14), showed essentially no difference between the reactions run with or without the incubation period. However, because of the ease to which electron deficient phenylboronic acids protodeboronate,[16] we were pleased to be able to prepare this biphenyl product in up to 66% yield. Indeed, in the ligandless reaction, only protodebornation occurs; while in the ligand assisted reactions, the competing protodeboronation reaction only became dominant after the 2 h. Fortunately, the volatile 1,3-difluorobenzene is easily separated from the product.

We are able to exploit the unique mild leaching property of Pd/C, to greatly reduce ligand loading by instituting incubation periods for electron donating aryl chlorides

Table 4. The effect of incubation time on the Pd/C-catalyzed Suzuki–Miyuara cross-couplings of aryl chlorides and aryl boronic acids[a]

Entry	X–C_6H_4Cl	Y–$B(OH)_2$	Ligand	Temp (°C)	Incubation time (h)	Post incubation time (h)	Yield[b] (%)
1	4-OCH_3	Phenyl	MePhos	80	3	21	63
2	4-OCH_3	Phenyl	MePhos	80	0	24	31
3	4-OCH_3	Phenyl	None	80	n/a	24	32
4	2-CH_3	Phenyl	XPhos	80	3	21	89
5	2-CH_3	Phenyl	XPhos	80	0	24	22
6	2-CH_3	Phenyl	None	80	n/a	24	15
7	2-CH_3	Phenyl	XPhos	100	0.25	2	90
8	2-CH_3	Phenyl	XPhos	100	0	2	24
9	2-CH_3	3-Pyridyl	XPhos	100	0.25	23	53
10	2-CH_3	3-Pyridyl	XPhos	100	0	23	45
11	2-CH_3	3-Pyridyl	None	100	n/a	23	0
12	4-OCH_3	2,4-Difluorophenyl[c]	XPhos	100	0.25	2	64
13	4-OCH_3	2,4-Difluorophenyl[c]	XPhos	100	0	2	66
14	4-OCH_3	2,4-Difluorophenyl[c]	None	100	n/a	2	0

[a] Reactions mixtures were incubated with 2.8 mmol aryl chloride, 3.4 mmol boronic acid, 5.6 mmol K_2CO_3, and 0.07 mmol 5% Pd/C in 20 mL of 20:1 (v/v) DMA:H_2O at 100 °C for 15 min, followed by continued heating in the presence of 0.3 mol % ligand.
[b] Isolated yield.
[c] Boronic acid (5.6 mmol) was used.

(2-chlorotoluene and 4-chloroanisole). However, for strongly electron withdrawing boronic acids (3-pyridylboronic acid and 2,4-difluorophenylboronic acid) incubation times were not necessary to achieve coupling at low ligand loadings. These results demonstrate that consideration of the properties of the aryl halide and the boronic acid may be effective in predicting if incubation times are necessary for Pd/C coupling at low ligand levels.

2.4. Catalyst recycling

A significant advantage of supported metal catalysts is that they can be easily removed from reaction mixtures. We have previously shown that Pd/C is no exception and simple filtration leads to high recovery of the Pd/C catalyst, which can be reused in subsequent reactions.[5h] However, palladium leaching caused by the presence of the ligand may render the catalyst inactive if the metal does not readsorb back onto the solid support. To address this issue, a catalyst recycling study was performed. The reaction between 2-chlorotoluene and *o*-tolylboronic acid using XPhos ligand (2.5 mol %) was repeated five times by recycling the same batch of Pd/C catalyst. No special precautions were taken to reactivate the Pd/C, except for the addition of 2.5 mol % fresh ligand. We found that the catalyst could be used twice without any loss in conversion (Table 5, entries 1 and 2) and up to four times with only a 10–20% (entries 3 and 4) loss. On the fifth use, a significant drop-off occurred resulting in a mere 18% conversion to product.

Recycled Pd/C that has been used with aryl chloride substrates may be less active because redeposition onto the carbon support leaves the palladium in a different form.[5c] However, especially in the case of the fifth run, the low conversion is also likely due to an accumulation of leaching in the preceding reactions.

2.5. Residual palladium determination

An important characteristic of supported metal catalysts is the low contamination of residual metal in the isolated products. To probe the issue of palladium leaching, four separate reactions were performed. In each case the catalyst was filtered, the products were isolated via simple precipitation or solvent removal, and the residual amount of palladium present was measured by atomic absorption spectroscopy.

As shown in Table 6, the palladium levels in the final products are substantially lower than that observed in some homogeneously catalyzed systems.[17] Moreover, palladium levels are near those we have observed for ligandless Pd/C reactions. This study and that of the above catalyst recycling study indicate that the low palladium contamination is a result of significant quantities that are redeposited back onto the carbon support during the reaction and leached palladium that is effectively washed away in the filtrate during workup.

Table 5. The effect of catalyst recycling on the XPhos assisted Pd/C-catalyzed Suzuki–Miyuara cross-coupling of 2-chlorotoluene and *o*-tolylboronic acid[a]

Number of times used	Conversion[b] (%)
1	73
2	70
3	60
4	53
5	18

[a] All reactions were performed with 1 equiv 2-chlorotoluene, 1.2 equiv *o*-tolylboronic acid, 2 equiv K_2CO_3, 0.025 equiv 5% Pd/C, and 0.025 equiv XPhos, in 20:1 (v/v) DMA:H_2O at 80 °C for 24 h.
[b] Corrected HPLC conversions are defined as (mmol 2,2′-dimethylbiphenyl)/(mmol 2-chlorotolene+mmol 2,2′-dimethylbiphenyl)×100.

Table 6. Residual palladium levels present in various biphenyl products obtained from the ligand assisted Pd/C-catalyzed Suzuki–Miyuara cross-coupling[a]

Entry	X–C_6H_4Cl	Y–$C_6H_4B(OH)_2$	Ligand (mol %)	Pd[b] (ppm)	Yield (%)
1	4-CN	4-CH_3	2.5[c]	9	95
2	4-CH_3	2-CH_3	2.5[d]	11	95
3	4-OCH_3	H	2.5[c]	30	58
4	4-OCH_3	H	0.25[c,e]	<5	60

[a] All reactions were performed with 3.0 mmol aryl chloride, 3.6 mmol aryl boronic acid, 6 mmol K_2CO_3, 0.075 mmol 5% Pd/C in 20 mL of 20:1 (v/v) DMA:H_2O, in the presence of the stated amount of ligand at 80 °C for 24 h, except where noted.
[b] Determined by Schwarzkopf Microanalytical Laboratory.
[c] MePhos.
[d] Xphos.
[e] The ligand was added after 3 h and heating was continued for 21 h.

2.6. Mercury poisoning tests

Originally mercury poisoning tests were developed to determine the presence of homogeneous transition metal species during the course of hydrogenation reactions.[18] Mercury can amalgamate with most metals, thereby disrupting the catalytic cycle and resulting in reaction cessation. Those processes affected by the presence of mercury are assumed to take place via a heterogeneous pathway. However, homogeneous metal species in higher oxidation states with tightly bound ligands are unaffected by mercury. More recent evidence has shown[7] that a positive mercury poisoning test only suggests the presence of a labile metal–ligand complex with the metal in the zero oxidation state.

To further address the issue of catalyst homogeneity we designed a series of experiments to determine the effect of mercury added to the reaction mixture. Both the ligandless Pd/C-catalyzed reaction between 4-chloroanisole and phenylboronic acid and the reaction run with 2.5 mol % ligand (Table 7, entries 1 and 2) were inhibited by the presence of excess mercury. In addition, to make certain that

Table 7. The effect of mercury on the Pd/C-catalyzed Suzuki–Miyuara cross-coupling of 4-chloroanisole and phenylboronic acid[a]

Entry	Procedure	Ligand (mol %)	Control conversion[b] (%)	Hg treated conversion[b] (%)
1	A	0	37	7
2	A	2.5	91	1
3	B	2.5	n.d.	1
4	C	2.5	38[c]	2

[a] See Section 4 for details.
[b] Corrected HPLC conversions are defined as (mmol 4-methoxybiphenyl)/(mmol 4-chloroanisole+mmol 4-methoxybiphenyl)×100.
[c] The conversion for the control reaction without mercury was equal to the conversion of the bulk reaction at 3 h (38%).

a palladium–ligand complex formed, the ligand assisted reaction (entry 3) was run for 3 h before the mercury was added. This protocol also resulted in catalyst poisoning.

According to the traditional interpretation of the mercury poisoning test, the results above imply that a heterogeneous reaction mechanism is operative. However, catalyst poisoning will also occur if the soluble palladium–ligand complex dissociates to give a free Pd(0) species. Therefore an experiment was designed (entry 4) whereby after 1 h of reaction at 100 °C aliquots were filtered through a 0.25 μM filter into gas tight syringes (to minimize contamination by oxygen). One aliquot was heated in the presence of excess mercury, while the other was heated without mercury to serve as a control. The control aliquot continued to form product at the same rate and in the same amount as the unfiltered bulk reaction. However, the aliquot treated with mercury failed to provide significant amounts of product (2% conversion) after the filtration. The control sample in this study indicates that a solubilized form of the catalyst is responsible for the catalysis. However, the fact that the mercury treated sample is poisoned indicates that the solubilized palladium is weakly ligated. This experiment provides additional evidence that the reaction takes place primarily via a homogeneous pathway.

2.7. Proposed catalytic cycle

Based on the results of the present study and building upon previously published findings, we propose the mechanism depicted in Figure 1 for the ligand assisted process. The initial palladium in Pd/C exists in the form of palladium hydroxide or oxide on the surface of the carbon support. It is reduced to Pd(0) by concomitant oxidation of the boronic acid[19,20] or by the DMA solvent. Oxidative addition to the aryl chloride results in the σ-aryl-Pd(II) chloride species, thereby desorbing the palladium from the carbon support.[6]

In the absence of ligand or at low ligand concentrations, this species can undergo reaction via the outer cycle shown in blue. Excess base present in the aqueous reaction mixture provides a source of hydroxide ions, which can displace the chloride to give the aryl-Pd(II) hydroxide species.[21] Transmetallation with the aryl boronic acid[22] and reductive elimination provide the product and regenerate Pd(0), which can either continue to react or readsorb onto the carbon support.

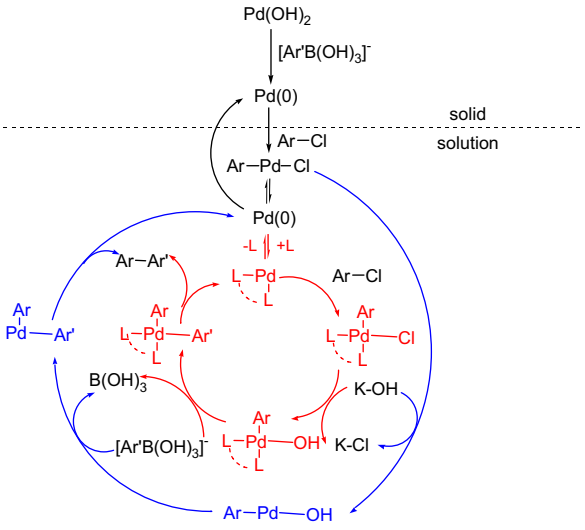


Figure 1. The proposed catalytic cycle for the ligand assisted Suzuki–Miyuara cross-coupling with Pd/C.

Mercury poisoning studies provide evidence for the presence of a labile palladium–ligand complex. We interpret this result to mean that the ligand association to Pd(0) is a reversible process. Ligand association results in the palladium–ligand complex, which may be monodentate or bidentate. This complex then proceeds via the inner cycle shown in red. This cycle also results in product and Pd(0), which as we have shown through palladium contamination studies, also undergoes the redeposition process.

One or both of the cycles may be operative at a time. For the ligand assisted reactions, the contribution of the outer cycle to product formation is likely minimal and the inner cycle is most likely the dominant pathway.

3. Conclusion

Unreduced, water wetted, Pd/C was shown to be an efficient precatalyst for the Suzuki–Miyuara reaction of aryl chlorides and aryl boronic acids. With the appropriate choice of ligand, substituted biphenyls can be prepared from substrates, which gave little or no yield under ligandless conditions. A particularly active catalyst system resulting from Pd/C and XPhos was utilized for the preparation of sterically hindered biphenyls. In some cases, by delaying the introduction of the ligand until palladium solubilization occurs, ligand turnover numbers could be significantly increased.

The ligand assisted system was examined through a series of experiments designed to determine if the catalyst retains any characteristics of ligandless heterogeneous systems or if it is simply a source of soluble palladium. The results of catalyst recycling experiments indicate that the Pd/C could be reused multiple times but rapidly became deactivated with the fifth reuse. Mercury poisoning tests imply the presence of a soluble zero valent molecular palladium species formed as a result of ligand dissociation. We propose a catalytic cycle in which ligand free and ligand assisted pathways combine to give practical yields of coupling products but also result in low levels of Pd contamination.

4. Experimental

4.1. Materials and methods

Palladium on carbon (5 wt %) was purchased from PMC (1610) (now a subsidiary of Johnson–Matthey) and Alfa Aesar, or obtained from Degussa (E 101 CA) and Engelhard corporations. We have found that unreduced, 50% water-wet with egg-shell dispersion perform best in these reactions. All other chemicals were purchased from Aldrich or Strem chemical companies and used without further purification. NMR spectra were recorded on a Varian Inova Spectrometer. Either Agilent series 1090 or 1100 HPLC systems were used to monitor reactions and check for purity. Conversions were

calculated by HPLC using calibrated curves of concentration versus absorbance of the appropriate reference. Preparative chromatography was either performed on a simple glass column packed with silica gel or on an Argonaut Flashmaster Solo using Isolute silica gel columns. Palladium analyses were performed by Schwarzkopf Microanalytical Laboratory. All isolated compounds were determined to be >97% pure by HPLC at 220 and 254 nm.

4.2. General Suzuki–Miyuara cross-coupling procedure

A 10 mL recovery flask containing a magnetic stir bar was charged with Pd/C (5 wt %, 50% water-wet, 85 mg, 0.02 mmol total Pd), aryl boronic acid (0.96 mmol), K_2CO_3 (221 mg, 1.60 mmol), ligand (0.02 mmol), and 20:1 v/v DMA:H_2O (5 mL). The mixture was degassed and purged with nitrogen and the aryl chloride was added (0.8 mmol). The reaction was heated at 80 °C for 24 h. The reaction mixture was filtered over Celite and washed with ethyl acetate. The ethyl acetate was then transferred to a separatory funnel and washed with water and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo.

4.2.1. 4-Methoxybiphenyl. The general procedure was followed with phenylboronic acid (120 mg, 0.96 mmol), 4-chloroanisole (97 μL, 0.8 mmol), and MePhos (7.3 mg, 0.02 mmol). The product was purified on silica gel (eluting with 2% ethyl acetate in hexane) to provide the title compound as a white powder (97 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56–7.51 (m, 4H), 7.43–7.40 (m, 2H), 7.32–7.28 (m, 1H), 7.00–6.97 (m, 2H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.1, 140.8, 133.7, 128.7, 128.1, 126.7, 126.6, 114.2, 55.3.

4.2.2. 4′-Methoxybiphenyl-4-carbaldehyde.[23] The general procedure was followed with 4-formylphenylboronic acid (144 mg, 0.96 mmol), 4-chloroanisole (97 μL, 0.8 mmol), and MePhos (7.3 mg, 0.02 mmol). The product was purified on an Isolute silica gel column using the Argonaut Flashmaster Solo (eluting with 0–100% methylene chloride in hexanes, linear gradient over 23 min) to provide the title compound as a white solid (50 mg, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.03 (s, 1H), 7.92 (dd, J=1.7, 6.5 Hz, 2H), 7.71 (d, J=8.2 Hz, 2H), 7.59 (dd, J=1.9, 6.7 Hz, 2H), 7.00 (dd, J=2, 6.7 Hz, 2H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.9, 160.1, 146.8, 134.7, 132.0, 130.3, 128.4, 127.0, 114.4, 55.4.

4.2.3. 4-Methylbiphenyl.[24] The general procedure was followed with phenylboronic acid (120 mg, 0.96 mmol), 4-chlorotoluene (95 μL, 0.8 mmol), and MePhos (7.3 mg, 0.02 mmol). The product was purified on silica gel (eluting with hexanes) to provide the title compound as a white solid (82 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61–7.55 (m, 2H), 7.51–7.47 (m, 2H), 7.44–7.39 (m, 2H), 7.31 (m, 1H), 7.24 (d, J=7.9 Hz, 2H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.1, 138.3, 137.0, 129.5, 128.7, 127.2, 127.0, 21.1.

4.2.4. 4-Formylbiphenyl.[25] The general procedure was followed with 4-formylphenylboronic acid (144 mg, 0.96 mmol), chlorobenzene (95 μL, 0.8 mmol), and MePhos (7.3 mg, 0.02 mmol). The product was purified on an Isolute silica gel column using the Argonaut Flashmaster Solo (eluting with 0–100% methylene chloride in hexanes, linear gradient over 23 min) to provide the title compound as a white solid (116 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.07 (s, 1H), 8.19 (d, J=8.3 Hz, 2H), 7.70 (d, J=8.3 Hz, 2H), 7.65 (d, J=7.4 Hz, 2H), 7.52–7.46 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.9, 147.2, 135.2, 130.3, 129.0, 128.4, 127.7, 127.3.

4.2.5. 2-Fluoro-4′-methylbiphenyl.[26] The general procedure was followed with 2-fluorophenylboronic acid (134 mg, 0.96 mmol), 4-chlorotoluene (95 μL, 0.8 mmol), and MePhos (7.3 mg, 0.02 mmol). The product was purified on an Isolute silica gel column using the Argonaut Flashmaster Solo (eluting with 0–2% methylene chloride in hexanes, linear gradient over 20 min) to provide the title compound as a colorless oil (105 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47–7.44 (m, 2H), 7.42 (dd, J=1.8, 7.8 Hz, 1H), 7.32–7.25 (m, 3H), 7.22–7.12 (m, 2H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.5, 130.7, 129.1, 128.9, 128.7, 128.6, 124.3, 116.1, 115.9, 21.2.

4.2.6. 2,4′-Dimethylbiphenyl.[27] The general procedure was followed with *o*-tolylboronic acid (130 mg, 0.96 mmol), 4-chlorotoluene (95 μL, 0.8 mmol), and XPhos (9.5 mg, 0.02 mmol). The product was purified on silica gel (eluting with hexanes) to provide the title compound as a colorless oil (132 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.26–7.21 (m, 8H), 2.40 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.8, 139.0, 136.3, 135.4, 130.2, 129.8, 129.0, 128.7, 127.0, 125.7, 21.1, 20.4.

4.2.7. 2-Methylbiphenyl.[26] The general procedure was followed with phenylboronic acid (120 mg, 0.96 mmol), 2-chlorotoluene (95 μL, 0.8 mmol), and XPhos (9.5 mg, 0.02 mmol). The product was purified on silica gel (eluting with hexanes) to provide the title compound as a colorless oil (95 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43–7.38 (m, 3H), 7.35–7.31 (m, 3H), 7.27–7.21 (m, 3H), 2.23 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.9, 135.3, 130.3, 129.8, 129.2, 128.0, 127.2, 126.7, 125.7, 20.4.

4.2.8. 2,2′-Dimethylbiphenyl.[25] The general procedure was followed with 2-methylphenylboronic acid (130 mg, 0.96 mmol), 2-chlorotoluene (95 μL, 0.8 mmol), and XPhos (9.5 mg, 0.02 mmol). The product was purified on silica gel (eluting with hexanes) to provide the title compound as a colorless oil (116 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27–7.20 (m, 6H), 7.10 (d, J=6.8 Hz), 2.06 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.6, 135.8, 129.8, 129.3, 127.1, 125.5, 19.8.

4.2.9. 2-Methoxy-2′-methylbiphenyl.[13] The general procedure was followed with *o*-tolylboronic acid (130 mg, 0.96 mmol), 2-chloroanisole (102 μL, 0.8 mmol), and XPhos (9.5 mg, 0.02 mmol). The product was purified on an Isolute silica gel column using the Argonaut Flashmaster Solo (eluting with 0–3% methylene chloride in hexanes, linear gradient over 20 min) to provide the title compound as a colorless oil (48 mg, 30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.31 (m, 1H), 7.26–7.12 (m, 5H), 7.03–6.94 (m, 2H), 3.68 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ:

131.0, 130.8, 129.6, 128.5, 127.3, 125.4, 120.4, 110.6, 55.4, 19.9.

4.2.10. 2,2′,6-Trimethylbiphenyl.[13] The general procedure was followed with *o*-tolylboronic acid (130 mg, 0.96 mmol), 2-chloro-*m*-xylene (112 mg, 0.8 mmol), and XPhos (9.5 mg, 0.02 mmol). The product was purified on silica gel (eluting with hexanes) to provide the title compound as a colorless oil (112 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33–7.23 (m, 3H), 7.11–7.21 (m, 3H), 7.06–7.02 (m, 1H), 1.99 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.0, 140.5, 135.9, 135.6, 130.0, 128.8, 127.2, 127.0, 126.9, 126.0, 20.3, 19.4.

4.2.11. 2′-Methylbiphenyl-4-carbaldehyde.[25] The general procedure was followed with 4-formylphenylboronic acid (144 mg, 0.96 mmol), 2-chlorotoluene (94 μL, 0.8 mmol), and XPhos (9.5 mg, 0.02 mmol). The product was purified on an Isolute silica gel column using the Argonaut Flashmaster Solo (eluting with 0–100% methylene chloride in hexanes, linear gradient over 23 min) to provide the title compound as a white crystalline solid (135 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.08 (s, 1H), 7.94 (d, J=8.0 Hz, 2H), 7.50 (d, J=8.0 Hz, 2H), 7.35–7.22 (m, 4H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 192.3, 148.7, 140.8, 135.4, 135.2, 130.8, 130.2, 130.0, 129.7, 128.3, 126.2, 20.6.

4.2.12. 2′,6′-Dimethyl-2-fluorobiphenyl.[13] The general procedure was followed with 2-fluorophenylboronic acid (134 mg, 0.96 mmol), 2-chloro-*m*-xylene (112 mg, 0.8 mmol), and XPhos (9.5 mg, 0.02 mmol). The product was purified on silica gel (eluted with hexanes) to provide the title compound as a colorless oil (140 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38–7.30 (m, 2H), 7.24–7.10 (m, 5H), 2.06 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.7, 136.6, 135.3, 131.3, 129.0, 128.9, 127.7, 127.2, 124.1, 115.8, 115.6, 20.4.

4.2.13. 2-Fluoro-4′-methoxybiphenyl.[13] The general procedure was followed with 2-fluorophenylboronic acid (134 mg, 0.96 mmol), 4-chloroanisole (97 μL, 0.8 mmol), and XPhos (9.5 mg, 0.02 mmol). The product was purified on silica gel (eluted with methylene chloride) to provide the title compound as a colorless oil (153 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52–7.48 (m, 2H), 7.42 (td, J=1.9, 7.7 Hz, 1H), 7.32–7.15 (m, 3H), 7.02–6.96 (m, 2H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.0, 159.2, 158.5, 130.5, 130.4, 130.1, 128.4, 128.3, 128.2, 124.3, 124.2, 116.1, 115.9, 115.2, 114.0, 113.9, 55.3.

4.3. Typical Suzuki–Miyuara cross-coupling procedure with low ligand loading (4-methoxybiphenyl)

A 100 mL Schlenk flask containing a magnetic stir bar was charged with Pd/C (340 mg, 5 wt %, 0.08 mmol total Pd, obtained from Degussa E 101 CA), phenylboronic acid (463 mg, 3.8 mmol) K_2CO_3 (884 mg, 6.40 mmol), and 20:1 v/v DMA:H_2O (20 mL). The mixture was degassed and purged with argon and 4-chloroanisole was added (388 μL, 3.2 mmol). The reaction was heated to 80 °C for 3 h, at which time MePhos (3 mg, 0.008 mmol) was added as a solid, while keeping positive argon pressure, and heating was continued for a further 21 h. The reaction mixture was filtered over Celite and washed with ethyl acetate. The ethyl acetate was then transferred to a separatory funnel and washed with water and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. Purification of the residue by silica gel chromatography yielded 383 mg (63% yield) of 4-methoxybiphenyl, which was identical to an authentic sample by ^{1}H NMR and HPLC.

4.3.1. 2-Methylbiphenyl. A 100 mL Schlenk flask containing a magnetic stir bar was charged with Pd/C (318 mg, 5 wt %, 0.075 mmol total Pd, obtained from Degussa E 101 CA), phenylboronic acid (489 mg, 3.6 mmol), K_2CO_3 (829 mg, 6.0 mmol), and 20:1 v/v DMA:H_2O (20 mL). The mixture was degassed, purged with argon, and 2-chlorotoluene was added (380 mg, 3.0 mmol). The reaction was heated to 80 °C for 3 h, and then XPhos (4 mg, 0.0084 mmol) was added as a solid, while keeping positive argon pressure and heating was continued for a further 21 h. The reaction mixture was filtered over Celite and washed with ethyl acetate. The ethyl acetate was then transferred to a separatory funnel and washed with water and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. Purification of the residue by silica gel chromatography yielded 450 mg (89% yield). ^{1}H NMR and HPLC were consistent with an authentic sample of the title compound.

4.3.2. 2-Methylbiphenyl. This compound was prepared according to the procedure above, except at a temperature of 100 °C with the XPhos added at 15 min and the reaction heated for a further 2 h. After purification a colorless oil was obtained (454 mg, 90%).

4.3.3. 3-(2-Methylphenyl)pyridine.[13] A 100 mL Schlenk flask containing a magnetic stir bar was charged with Pd/C (298 mg, 5 wt %, 0.07 mmol total Pd, obtained from Degussa E 101 CA), 3-pyridylboronic acid (516 mg, 4.2 mmol), K_2CO_3 (774 mg, 5.6 mmol), and 20:1 v/v DMA:H_2O (20 mL). The mixture was degassed, purged with argon, and 2-chlorotoluene added (328 μL, 2.8 mmol). The reaction was heated to 100 °C for 15 min, and then XPhos (4 mg, 0.0084 mmol) was added as a solid, while keeping positive argon pressure, and heating was continued for a further 23 h. The reaction mixture was filtered over Celite and washed with ethyl acetate. The ethyl acetate was then transferred to a separatory funnel and washed with water and brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. The resulting residue was purified on silica gel (eluting with 10% ethyl acetate in hexane, followed by 33% ethyl acetate in hexane) to provide the title compound as a colorless oil (249 mg, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.60 (dd, J=1.6, 4.9 Hz, 2H), 7.65 (dt, J=7.8, 1.9 Hz, 1H), 7.36–7.26 (m, 4H), 7.21 (d, J=7 Hz), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.9, 148.1, 136.4, 135.5, 130.5, 129.8, 128.1, 126.1, 123.0, 20.3.

4.3.4. 2,4-Difluoro-4′-Methoxybiphenyl.[13] A 100 mL Schlenk flask containing a magnetic stir bar was charged with Pd/C (298 mg, 5 wt %, 0.07 mmol total Pd, obtained from Degussa E 101 CA), 2,4-difluorophenylboronic acid (884 mg, 5.6 mmol), K_2CO_3 (774 mg, 5.6 mmol), and 20:1 v/v DMA:H_2O (20 mL). The mixture was degassed, purged

with argon, and 4-chloroanisole added (340 μL, 2.8 mmol). The reaction was heated to 100 °C for 15 min, and then XPhos (4 mg, 0.0084 mmol) was added as a solid, while keeping positive argon pressure, and heating was continued for a further 2 h. The reaction mixture was filtered over Celite and washed with ethyl acetate. The ethyl acetate was then transferred to a separatory funnel and washed with water and brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. The resulting residue was purified on silica gel (eluting with 2% ethyl acetate in hexane) to provide the title compound as a colorless oil (392 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45 (d, J=8.5 Hz, 2H), 7.38 (q, J=15.0, 8.4 Hz, 1H), 6.99 (d, J=8.7 Hz, 2H), 6.97–6.90 (m, 2H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.2, 163.1, 160.7, 160.6, 159.2, 158.2, 131.2, 131.1, 131.0, 130.0, 129.7, 129.3, 127.3, 115.2, 115.1, 114.0, 111.5, 111.4, 111.3, 104.5, 104.2, 104.0, 55.3.

4.4. Catalyst recycling

The procedure for the initial reaction in this section is described in Section 4.2 above, except it was performed on a 3 mmol scale relative to the aryl chloride. All additional reactions were scaled according to the amount of Pd/C that was recovered. A Schlenk flask containing a magnetic stir bar was charged with Pd/C (5 wt %, 50% water-wet, 0.025 equiv total Pd), *o*-tolylboronic acid (1.2 equiv), K_2CO_3 (2 equiv), XPhos (0.025 equiv), and 20:1 v/v DMA:H_2O. The mixture was degassed and purged with nitrogen and 2-chlorotoluene was added (1 equiv). The reaction was heated at 80 °C for 24 h. The reaction mixture was filtered through filter paper, washed with water and acetone, and allowed to air dry for 1 h. The Pd/C was then carefully scraped from the filter paper and used as is in the next reaction. Product conversions were determined by HPLC.

4.5. Typical residual palladium determination experiment (Table 5, entry 3)

A 100 mL round bottom flask containing a magnetic stir bar was charged with Pd/C (5 wt %, 50% water-wet, 340 mg, 0.08 mmol total Pd), phenylboronic acid (463 mg, 3.8 mmol), K_2CO_3 (884 mg, 6.40 mmol), MePhos (29 mg, 0.08 mmol), and 20:1 v/v DMA:H_2O (20 mL). The mixture was degassed and purged with nitrogen and 4-chloroanisole was added (388 μL, 3.2 mmol). The reaction was heated at 80 °C for 24 h. The reaction mixture was filtered through filter paper and washed water and acetone. The solution was filtered again through a 0.45 μM filter and the filtrate was poured into 250 mL of water. The precipitate was collected on filter paper and washed with water. After drying under high vacuum the sample was sent for analysis by atomic absorption.

4.5.1. 4-Methylbiphenyl-4-carbonitrile.[28] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 (q, J=8.5, 17.2 Hz, 4H), 7.49 (d, J=8.1 Hz, 2H), 7.28 (d, J=8.5 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.84, 139.0, 136.5, 132.8, 130.1, 127.7, 127.3, 119.3, 110.8, 21.4.

4.6. Mercury poisoning test: procedure A

A 500 mL baffled flask equipped with an overhead stirrer was charged with Pd/C (5 wt %, 50% water-wet, 340 mg, 0.08 mmol total Pd), phenylboronic acid (463 mg, 3.8 mmol), K_2CO_3 (884 mg, 6.40 mmol), MePhos (29 mg, 0.08 mmol), mercury (approximately 500 mg), and 20:1 v/v DMA:H_2O (20 mL). The mixture was degassed and purged with argon and 4-chloroanisole was added (388 μL, 3.2 mmol). The reaction was stirred at 1000 rpm and heated to 80 °C for 24 h. Product conversion was determined by HPLC.

4.7. Mercury poisoning test: procedure B

A 500 mL baffled flask equipped with an overhead stirrer was charged with Pd/C (5 wt %, 50% water-wet, 340 mg, 0.08 mmol total Pd), phenylboronic acid (463 mg, 3.8 mmol), K_2CO_3 (884 mg, 6.40 mmol), MePhos (29 mg, 0.08 mmol), and 20:1 v/v DMA:H_2O (20 mL). The mixture was degassed and purged with argon and 4-chloroanisole was added (388 μL, 3.2 mmol). The reaction was stirred at 1000 rpm and heated at 80 °C for 3 h. While keeping positive argon pressure, mercury (approximately 500 mg) was added. The reaction was heated for a further 21 h at 80 °C. Product conversion was determined by HPLC.

4.8. Mercury poisoning test: procedure C

A 500 mL baffled flask equipped with an overhead stirrer was charged with Pd/C (5 wt %, 50% water-wet, 340 mg, 0.08 mmol total Pd), phenylboronic acid (463 mg, 3.8 mmol), K_2CO_3 (884 mg, 6.40 mmol), MePhos (29 mg, 0.08 mmol) and 20:1 v/v DMA:H_2O (20 mL). The mixture was degassed and purged with argon and 4-chloroanisole was added (388 μL, 3.2 mmol). The reaction was stirred at 1000 rpm and heated at 100 °C for 1 h. Two aliquots were removed via syringes fitted with a 0.25 μM filter. One aliquot was heated at 100 °C in the presence of excess mercury (~50 mg) and the other was heated at 100 °C without mercury. Both aliquots and the bulk reaction were heated for an additional 3 h at 100 °C. Product conversion was determined by HPLC.

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