

An improved protocol for ligandless Suzuki–Miyaura coupling in water

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Abstract—Using a reverse order of addition of reagents, PdCl₂ and Pd(OAc)₂ are efficient catalysts for the Suzuki–Miyaura reactions in water. The ligandless and mild conditions, the high stability of the catalytic system, short reaction time and good to excellent yields are important features of this protocol.

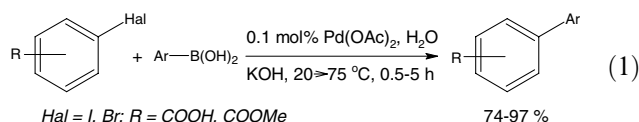
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The palladium-catalyzed cross-coupling of aryl halides with arylboronic acids, the Suzuki–Miyaura reaction,¹ represents a straightforward and highly effective method for carbon–carbon bond formation in the synthesis of biaryl compounds. Although many efficient palladium catalysts with novel P- and N-ligands have been discovered for the reaction,² also of great importance are the protocols that utilize ‘ligandless’ Pd-catalysts in water or aqueous media.³ Water has clear advantages as a solvent for use in this type of reactions because it is cheap, readily available, and nontoxic.⁴ There are, however, problems associated with low stability of ligandless catalytic systems. To the best of our knowledge, the efficiency of ligandless Pd catalysts for the coupling of sterically hindered arylboronic acids and aryl halides has not been investigated sufficiently.⁵ It is known that the cross-coupling of sterically hindered arylboronic acids proceeds slowly and gives lower yields due to steric hindrance and hydrolytic deboronation.⁶ It is also noteworthy that the cross-coupling of sterically hindered substrates⁷ can be used as a very sensitive test for the efficiency of catalytic systems.

We report herein that it is possible to increase the stability of ligandless Pd-catalysts by simply changing the order of addition of the reagents and perform the Suzuki–Miyaura reactions of water soluble and insoluble substrates in neat water under comparatively mild conditions (Eq. 1).

Keywords: Suzuki–Miyaura reaction; Ligandless palladium; Biaryls; Catalysis.

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Continuing our investigations on the application of ligandless palladium catalysts, we initially studied the reaction of mesitylboronic acid [MesB(OH)₂] with 4-iodobenzoic acid in water as a model system under gradual heating from 20 to 75 °C in the presence of 0.1 mol % of PdCl₂ (0.1 M water solution) and 3 equiv of various bases [Na₂CO₃, K₂CO₃, K₃PO₄, Ba(OH)₂, NaOH and KOH]. In the presence of bases, 4-iodobenzoic acid was converted into the corresponding water soluble benzoate and the reactions proceeded under homogeneous conditions. An important observation made during a control experiment (no catalyst present) was that MesB(OH)₂ decomposed quantitatively to mesitylene under the reaction conditions after 1.5–2 h. The results are recorded in Table 1, and show that the bases used have dramatic effects on the yields of the cross-coupling product. Of the bases tested, only NaOH and KOH resulted in high coupling yields after 1 h (entries 1–6). Presumably the increase of the reaction yields in the presence of strong bases can be attributed to the easy formation of the trihydroxyarylboronate [MesB(OH)₃][−]—the key intermediate at the transmetalation step.^{1a,8} All reaction mixtures became dark, a precipitate of Pd-black began to deposit in the early stages of the reactions, and the reactions stopped before full conversion. A large excess of MesB(OH)₂ did not improve the yield of coupling product (entries 9 and 10). It was shown that the cross-coupling of MesB(OH)₂ did not proceed in

Table 1. Cross-coupling of mesitylboronic acid with 4-iodobenzoic acid^a

| Entry | Catalyst | Base | Time (h) | Yield ^b (%) |
|-------------------|--------------------------------|---------------------------------|----------|------------------------|
| 1 | PdCl ₂ | Na ₂ CO ₃ | 2 | 0 |
| 2 | PdCl ₂ | K ₂ CO ₃ | 2 | 0 |
| 3 | PdCl ₂ | K ₃ PO ₄ | 2 | 49 |
| 4 | PdCl ₂ | Ba(OH) ₂ | 2 | 55 |
| 5 | PdCl ₂ | NaOH | 1 | 88 |
| 6 | PdCl ₂ | KOH | 1 | 79 |
| 7 | PdCl ₂ ^c | KOH | 2 | 44 |
| 8 | PdCl ₂ ^d | KOH | 1 | 84 |
| 9 ^e | PdCl ₂ | KOH | 2 | 74 |
| 10 ^f | PdCl ₂ | KOH | 2 | 81 |
| 11 | PdCl ₂ ^g | KOH | 1 | 100 |
| 12 | PdCl ₂ ^h | KOH | 1 | 59 |
| 13 ⁱ | PdCl ₂ | KOH | 1 | 100 ^j |
| 14 ⁱ | PdCl ₂ ^c | KOH | 0.5 | 97 |
| 15 | Pd(OAc) ₂ | KOH | 1 | 100 |
| 16 ^{i,k} | Pd(OAc) ₂ | KOH | 1 | 100 |
| 17 ^{i,l} | Pd(OAc) ₂ | KOH | 2 | 43 |
| 18 ^{i,m} | Pd(OAc) ₂ | KOH | 2 | 14 |
| 19 | PdCl ₂ (dppf) | KOH | 1 | 100 |
| 20 | Pd-black | KOH | 2 | 0 |

^a 1 mmol of ArI, 1.05 mmol of MesB(OH)₂, 3 mmol of base, 5 mL of water, 0.1 mol % PdCl₂ (0.1 M water solution), gradual heating from 20 to 75 °C, argon.

^b Determined from the ¹H NMR spectra of the crude samples.

^c 1 mol % PdCl₂.

^d 0.01 mol % PdCl₂.

^e 1.5 equiv of MesB(OH)₂.

^f 2.5 equiv of MesB(OH)₂.

^g Solution of PdCl₂ (0.1 M) and palmitic acid (1 M) in acetic acid.

^h Solid.

ⁱ Base was added after reagents and catalyst.

^j Isolated yield was 96%.

^k 3-IC₆H₄COOH was used.

^l 2-IC₆H₄COOH was used.

^m 4-BrC₆H₄COOH was used.

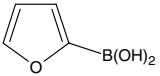
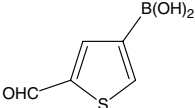
the presence of Pd-black as catalyst (entry 20). Earlier, we reported that Pd-black was an active catalyst for the Suzuki–Miyaura reaction of sterically unhindered substrates in water.⁹ The reaction can be carried out at lower catalyst loading. For example, the coupling in the presence of 0.01 mol % of PdCl₂ for 1 h provided an 84% yield of the product.¹⁰ However, high catalyst loading (1 mol %) reduced the coupling yield (entries 7 and 8). In this case, the formation of Pd-black was clearly visible. A similar effect of Pd-loading on product yield and palladium black precipitation was recently observed in a Heck reaction in the presence of ligandless palladium^{10c,d} and was explained in terms of the equilibrium between Pd(0)-species, soluble palladium clusters and Pd-black: low Pd concentrations suppress the aggregation of palladium into inactive Pd-black and keep the majority of the metal available for catalysis. Surprisingly, we have found that the formation of Pd-black also depends on the reactivity of arylboronic acid during transmetallation step. For example, the reaction of 4-iodobenzoic acid with the more reactive 4-methoxyphenylboronic acid in the presence of 1 mol % of PdCl₂ proceeded without Pd-black formation up to full conversion of the aryl iodide (20 °C, 5 min, 100% yield by ¹H NMR). We can hypothesize that under ligandless

conditions oxidative addition of ArI to Pd(0) with the formation of an [ArPd(II)I]-complex proceeds reversibly, and, if a transmetallation step is fast, equilibrium shifts towards the Pd(II)-species thereby suppressing Pd-black formation.

A considerable improvement in the yield, up to quantitative, was obtained when the reaction was carried out in the presence of 0.1 mol % of PdCl₂ and 1 mol % of palmitic acid (entry 11) or 0.1 mol % of Pd(OAc)₂ (entry 15). The reverse order of addition of reagents, when base was added after arylboronic acid, aryl halide, water and catalyst,¹¹ also resulted in a quantitative product yield in the presence of PdCl₂ (entry 13). The reaction proceeded smoothly without Pd-black formation even at higher catalyst loading (1 mol % of PdCl₂) (entry 14). The facts that neither Pd-black was observed, nor did the reaction stop halfway, indicated that the stability of the ligandless catalytic system increased considerably in these cases. When the solution of PdCl₂ was stirred with suspension of 4-iodobenzoic acid in water, the yellow-brown colour of the mixture disappeared in 5 min and the palladium salt adsorbed on the surface of the aryl iodide to form presumably the PdCl₂(ArI)_n complexes. We may suppose that after addition of arylboronic acid and base a reduction of Pd(II) by the trihydroxyarylboronate [MesB(OH)₃][−] results in the formation of Pd(0)(ArI)_n particles. Subsequent intramolecular oxidative addition in these complexes proceeds rapidly and aggregation of Pd(0)-species to form inactive Pd-black is suppressed. Under these conditions, in the presence of Pd(OAc)₂, 3-iodobenzoic acid also reacted smoothly to give the cross-coupling product in high yield (entry 16). 4-Bromobenzoic acid was found to be inactive under the conditions studied (entry 18). It is interesting to note that the complex PdCl₂(dppf) afforded a quantitative yield in 1 h (entry 19).

To verify the effectiveness of this procedure, the reactions of various arylboronic acids with 2-iodobenzoic acid were examined using 0.1 mol % of Pd(OAc)₂ as catalyst, H₂O as solvent, and KOH as base (the base was added after the reagents, water and catalyst) and gradual heating from 20 to 75 °C (Table 2). Previously, there have been no reported cross-coupling reactions of 2-iodo(bromo)benzoic acids in high yields.^{3e,12} As shown in Table 2 (entries 1–5), the reactions of 2-iodobenzoic acid with 2-, 3- and 4-methylphenyl- and 2- and 4-methoxyphenyl-boronic acids gave the cross-coupling products in high yields in 4–5 h. Even sterically hindered MesB(OH)₂ reacted with 2-iodobenzoic acid in 2 h, yielding 36% of 2-mesitylbenzoic acid (entry 6). In a control experiment, where the catalyst was added after reagents, water and base, reaction of 4-methoxyphenylboronic acids and 2-iodobenzoic acid stopped before full conversion (1 h—58%, 6 h—62% yield by ¹H NMR). A considerable improvement in the yield in the case of mesitylboronic acid was obtained when the reaction was carried out with methyl 2-iodobenzoate (entry 8). Since methyl 2-iodobenzoate was insoluble in water, hence the reaction proceeded heterogeneously (however, the addition of TBAB was not required^{3f}), and hydrolysis of the ester was minimal. The reactions of

Table 2. Synthesis of 2-arylbenzoic acids and their methyl esters^a

| Entry | ArI | Ar'B(OH) ₂ | Time (h) | Yield ^b (%) |
|-------------------|--|---|----------|------------------------|
| 1 | 2-IC ₆ H ₄ COOH | 2-MeC ₆ H ₄ B(OH) ₂ | 5 | 78 |
| 2 | 2-IC ₆ H ₄ COOH | 3-MeC ₆ H ₄ B(OH) ₂ | 4 | 93 |
| 3 | 2-IC ₆ H ₄ COOH | 4-MeC ₆ H ₄ B(OH) ₂ | 4.5 | 84 |
| 4 | 2-IC ₆ H ₄ COOH | 2-MeOC ₆ H ₄ B(OH) ₂ | 4 | 95 |
| 5 | 2-IC ₆ H ₄ COOH | 4-MeOC ₆ H ₄ B(OH) ₂ | 5 | 93 |
| 6 | 2-IC ₆ H ₄ COOH | MesB(OH) ₂ | 2 | 36 (43) ^c |
| 7 | 2-IC ₆ H ₄ COOH | 4-CF ₃ C ₆ H ₄ B(OH) ₂ | 4 | 92 |
| 8 | 2-IC ₆ H ₄ COOMe | MesB(OH) ₂ | 2 | (75) ^c |
| 9 | 2-IC ₆ H ₄ COOMe | 2-MeC ₆ H ₄ B(OH) ₂ | 1 | 94 |
| 10 ^{d,e} | 2-IC ₆ H ₄ COOMe | 2-MeC ₆ H ₄ B(OH) ₂ | 0.5 | 97 |
| 11 | 2-IC ₆ H ₄ COOMe | 4-FC ₆ H ₄ B(OH) ₂ | 1 | 93 |
| 12 ^d | 2-IC ₆ H ₄ COOMe | 4-FC ₆ H ₄ B(OH) ₂ | 0.5 | 89 |
| 13 ^d | 2-IC ₆ H ₄ COOMe |  | 1 | 94 |
| 14 ^d | 2-IC ₆ H ₄ COOMe |  | 1 | 95 |

^a 1 mmol of ArI, 1.05 mmol of Ar'B(OH)₂, 0.1 mol % Pd(OAc)₂, 5 mL of water, 3 mmol of KOH, gradual heating from 20 to 75 °C, argon.

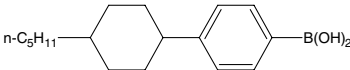
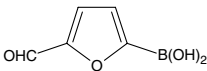
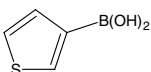
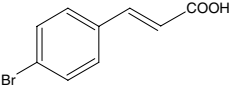
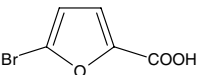
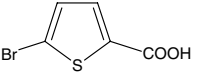
^b Isolated yield.

^c ¹H NMR yield.

^d 0.1 mol % PdCl₂(dppf).

^e After alkaline hydrolysis in ethanol solution, pure acid was isolated in 88% yield.

Table 3. Cross-coupling reactions under the improved protocol^a

| Entry | ArHal | Ar'B(OH) ₂ | Time (h) | Yield ^b (%) |
|----------------|---|--|----------|------------------------|
| 1 | 4-IC ₆ H ₄ COOH | MesB(OH) ₂ | 1 | 77 |
| 2 | 4-IC ₆ H ₄ COOH | 2-MeOC ₆ H ₄ B(OH) ₂ | 1 | 95 |
| 3 | 4-IC ₆ H ₄ COOH |  | 1 | 81 |
| 4 | 4-IC ₆ H ₄ COOH |  | 2 | 79 |
| 5 | 3-IC ₆ H ₄ COOH | MesB(OH) ₂ | 1.5 | 82 |
| 6 | 3-IC ₆ H ₄ COOH | 2-MeOC ₆ H ₄ B(OH) ₂ | 1 | 92 |
| 7 ^c | 3-IC ₆ H ₄ COOH |  | 1 | 97 |
| 8 | 4-BrC ₆ H ₄ COOH | 3-MeC ₆ H ₄ B(OH) ₂ | 1 | 90 |
| 9 | 4-BrC ₆ H ₄ COOH | 4-MeC ₆ H ₄ B(OH) ₂ | 1 | 86 |
| 10 |  | 4-CF ₃ C ₆ H ₄ B(OH) ₂ | 2 | 83 |
| 11 |  | 4-MeC ₆ H ₄ B(OH) ₂ | 40 min | 74 |
| 12 |  | 4-MeC ₆ H ₄ B(OH) ₂ | 1 | 92 |

^a 1 mmol of ArHal, 1.05 mmol of Ar'B(OH)₂, 0.1 mol % Pd(OAc)₂, 5 mL of water, 3 mmol of KOH, gradual heating from 20 to 75 °C, argon.

^b Isolated yield.

^c 0.1 mol scale, 0.001 mol % Pd(OAc)₂.

unhindered aryl- and heteroarylboronic acids with methyl 2-iodobenzoate were also examined. Each reaction proceeded to full conversion of the aryl iodide in the presence of 0.1 mol % of Pd(OAc)₂ or PdCl₂(dppf) in 0.5–1 h giving methyl 2-aryl(heteroaryl)benzoates in 89–97% isolated yields (entries 9–14). A substrate with the strong base-sensitive CHO-group was also tolerated (entry 12).

The value of our protocol was illustrated by a one-step synthesis of 2-(4-trifluoromethylphenyl)benzoic acid (xenalipin), an active pharmaceutical ingredient which lowers cholesterol and triglyceride levels in plasma.¹³ Coupling of 2-iodobenzoic acid with 4-trifluoromethylphenylboronic acid in the presence of 0.1 mol % of Pd(OAc)₂ afforded xenalipin in 92% isolated yield in 4 h (entry 7).

These standard conditions¹⁴ were successfully used in the reactions of various bromo(iodo)benzoic acids and their heterocyclic analogs with aryl(heteroaryl)boronic acids to give cross-coupling products in high yields in 1–2 h (Table 3). For preparative scale synthesis, the catalyst amount was reduced to a 10 ppm level without a decrease in activity. For instance, 3-iodobenzoic acid reacted with 3-thienylboronic acid (entry 7) in 97% isolated yield in 1 h, corresponding to turnover numbers (TON) up to 97,000 and turnover frequencies (TOF) up to 97,000 h⁻¹.

It is important to note that the end of all these reactions (Tables 1–3) was clearly visualized since palladium metal precipitated as soon as all of the aryl halide was consumed and pale yellow-brown mixtures turned dark. Crude products were in most cases sufficiently pure (>97% by ¹H NMR). Pure products were obtained by simple filtration through silica gel using ether as solvent to remove traces of Pd-black.

In summary, we have found that under modified conditions ligandless PdCl₂ and Pd(OAc)₂ are effective catalysts for Suzuki–Miyaura coupling of aryl iodides and bromides at low palladium loading in water.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.04.039.

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14. *Typical procedure for cross-coupling reactions.* A mixture of 1 mmol of aryl halide, 5 ml of water, 1.05 mmol of arylboronic acid and 0.001 mmol (0.1 mol %, 0.22 mg) of

$\text{Pd}(\text{OAc})_2$ was stirred at rt for 5 min under argon, followed by the addition of 3 mmol (0.168 g) of KOH. The temperature was gradually (over ~1 h) increased up to 75 °C. The mixture was stirred for the appropriate time and conditions (Tables 1–3). After the reaction had been completed the mixture was acidified (in the case of acids) and the product was extracted by ether. Pure products were obtained by filtration of the ether solution through silica gel and evaporation of solvent.