

Base- and ligand-free heterogeneously catalyzed homocoupling of arylboronic acids

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Abstract

Homocoupling of arylboronic acids was successfully carried out by Pd/C in water/2-propanol (9:1 volume ratio) under air to obtain symmetric biaryls in good yield. The base-free, ligand-free system and the heterogeneous nature of the catalysts allow for a practical and environmentally friendly operation. The influence of the co-solvent ratio and the reaction temperature was studied. The catalyst showed increasing activity when the fraction of water in the H₂O/2-propanol mixture was increased from 10% to 90%; also, a lower reaction temperature led to a slightly faster protodeboronation of phenylboronic acid. Furthermore, the effect of introducing functional groups on the phenyl ring was explored. DFT calculations indicate that the presence of sulfur in the functional group hinders Pd catalysis and results in a slow reaction. The calculations also suggest that the overall reactivity of the different arylboronic acids is independent of the first reaction step, the oxidative addition of Pd to the arylboronic acid. © 2008 Elsevier B.V. All rights reserved.

Keywords: Homocoupling; Arylboronic acids; Pd; Heterogeneous catalysis; DFT calculations

1. Introduction

Homocoupling of arylboronic acids, also called “Suzuki-type self-coupling reactions” [1,2], provides a straightforward method to synthesize symmetrical biaryls, which are important building blocks for natural products, ligands employed in catalysis and active pharmaceutical ingredients (APIs). Examples include steganone [3], chiral 6,6'-bis(oxazolyl)-1,1'-biphenyls [4] and glucocorticoid receptor antagonists [5]. Typically, the homocoupling of arylboronic acids is carried out using homogeneous Pd catalysts with bases and/or oxidants dissolved in organic solvents or solvent mixtures [6–12]. In recent years, several water-based catalytic systems for the homocoupling of arylboronic acids were developed [13–15]. For example, Kabalka and Wang [13] introduced a system based on PdCl₂, Na₂CO₃ and *p*-toluenesulfonyl chloride in water. Cravotto et al. [14] reported the catalytic activity of a system including

Pd/C and KF in water in combination with high-intensity ultrasound.

Although, the known catalytic systems give excellent yields, several disadvantages exist: (1) the ligands of the homogeneous catalysts may react to form undesired products, such as mono-substituted biaryls (R–Ph–Ph–H); (2) homogeneous catalysts are difficult to recover and to reuse; (3) the required additional reagents increase costs; (4) the use of some organic solvents, such as toluene and dimethylether, poses environmental concerns. A novel system that eliminates these disadvantages, would be ideal for the synthesis of biaryls in terms of economics and efficiency.

Previously, we carried out a detailed mechanistic investigation of Pd-leaching from heterogeneous Pd/C catalysts during Suzuki coupling reactions [16]. During these studies, we observed homocoupling of phenylboronic acids occurring in a mixture of phenylboronic acid **1** and water/2-propanol (9:1 volume ratio) with Pd/C at 75 °C under air. Further investigation showed excellent yields of biphenyl **2**, reaching 50% and 92% after 30 min and 2 h, respectively (Fig. 1); in addition, small amounts of benzene **3** and phenol **4** were observed. The latter species are formed by protodeboronation of phenyl-

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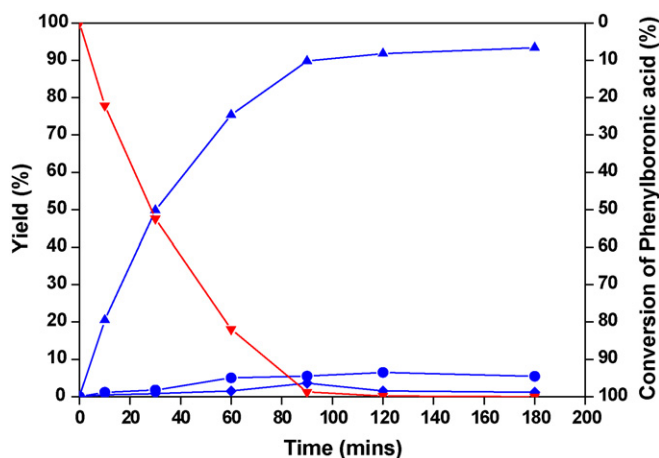
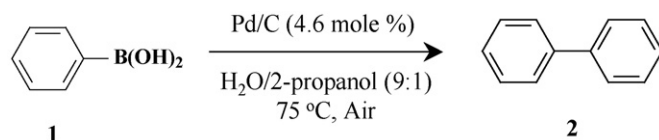


Fig. 1. Conversion of phenylboronic acid (\blacktriangledown) and yields of biphenyl (\blacktriangle), benzene (\bullet) and phenol (\square) as a function of time. Reaction conditions: 0.64 mmole phenylboronic acid and 4.6 mole% Pd/C in 10 mL water/2-propanol (9:1 volume ratio) at 75 °C.

boronic acid, a side reaction of arylboronic acids occurring in water or alcohols. The rate of protodeboronation is a function of the arylboronic acid type, the reaction solvent and the reaction temperature [7,17,18].

This catalytic system offers significant potential and provides several advantages for homocoupling of arylboronic acids under base- and ligand-free conditions. First, no extra reagents are needed, thus simplifying the overall reaction at reduced cost. Second, Pd/C is a reusable catalyst. For example, Sakurai et al. [19] studied the Suzuki coupling of 4-iodophenol and phenylboronic acid in water and reported a 89% yield of the desired product even during the sixth run. Furthermore, the absence of any ligands on the transition metal catalyst should prevent the formation of undesired biaryls. The goal of this contribution is to provide more detailed understanding of Pd/C-catalyzed homocoupling reactions, using the model coupling of biphenyls shown in Scheme 1, and to optimize the reaction conditions



Scheme 1. Model reaction for base- and ligand-free Pd/C-catalyzed homocoupling of aryl-boronic acids.

in order to allow for a straightforward industrial implementation.

2. Experimental

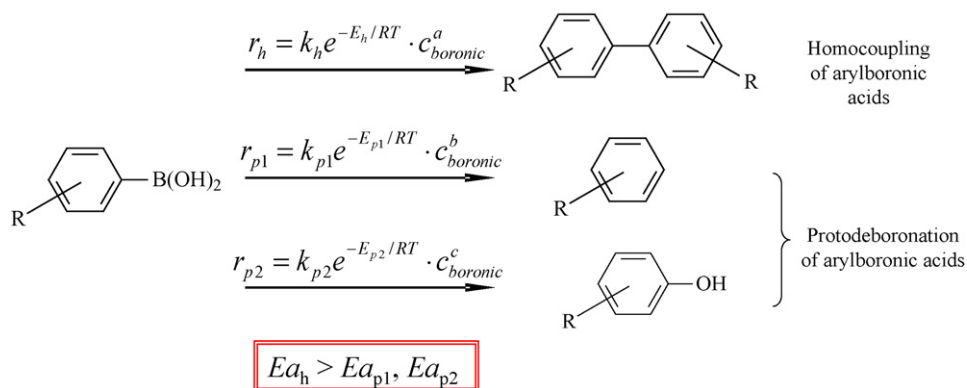
The model coupling reaction of biphenyl was carried out in a 100 mL round-bottom glass reactor equipped with a stirring bar (1 cm length). Phenylboronic acid (0.64 mmol) was added to 10 mL reaction solvent (water/2-propanol in 9:1 volume ratio) at room temperature, while vigorously stirring for 15 min. After adding Pd/C (5 wt.%, Degussa, 50% water-wet, amount of catalyst: 4.6 mole% of Pd with respect to the molar amount of phenylboronic acid), the reaction mixture was heated to 75 °C to carry out the reaction. After 3 h, Pd/C was removed by filtration through a 0.45 μ m filter (Fisher brand), and the Pd/C filter cake was washed using 2-propanol (2×35 mL). The filtrate was analyzed by high-performance liquid chromatography (HPLC) to determine the concentrations of **1** (reagent), **2** (product) as well as **3** and **4** (side products), respectively. HPLC analyses were performed on a Shimadzu SP-10 liquid chromatograph equipped with a UV-vis absorption detector and an Agilent zorbax eclipse XDB-C8 column. The HPLC mobile phase program was: (a) 0–9 min, 60% deionized water with 0.05% formic acid and 40% acetonitrile (volume ratios), and (b) 9–30 min, 40% deionized water with 0.05% formic acid and 60% acetonitrile. The flow rate of the mobile phase was 1.2 mL/min. The wavelengths of the detection light were set from 190 to 250 nm. The conversion of **1** and the yields were calculated from the measured concentrations

Table 1
Optimization of conditions for Pd/C-catalyzed homocoupling reactions of phenylboronic acid

Entry	Conditions ^a	Reaction time (h)	Conversion of 1 (%)	Yield 2 (%)	Yield 3 (%)	Yield 4 (%)
1	9:1 ^b , 75 °C, 4.6 mole% Pd/C	3	100	93	6	1
2	7:3, 75 °C, 4.6 mole% Pd/C	3	99	91	3	5
3	5:5, 75 °C, 4.6 mole% Pd/C	3	83	74	6	2
4	3:7, 75 °C, 4.6 mole% Pd/C	3	54	49	4	1
5	1:9, 75 °C, 4.6 mole% Pd/C	3	19	16	2	1
6	Water, 75 °C, 4.6 mole% Pd/C	2	>99	92	6	1
7	9:1, 85 °C, 4.6 mole% Pd/C	3	100	93	6	1
8	9:1, 65 °C, 4.6 mole% Pd/C	3	>99	90	4	6
9	9:1, 55 °C, 4.6 mole% Pd/C	3	>99	88	7	5
10	9:1, 45 °C, 4.6 mole% Pd/C	3	82	72	5	5
11	9:1, RT, 4.6 mole% Pd/C	3	21	18	2	1
12	9:1, RT, 4.6 mole% Pd/C	24	98	88	4	6
13	9:1, 75 °C, 9.2 mole% Pd/C	1	100	94	5	<1
14	9:1, 75 °C, 2.3 mole% Pd/C	2	89	78	4	7
15	9:1, 75 °C, 4.6 mole% Pd(OAc) ₂	3	47	42	1	4

^a Basic parameters: 0.64 mmol phenylboronic acid and 10 mL water/2-propanol solvent.

^b Volume ratio of water/2-propanol solvent.



Scheme 2. Competition between homocoupling and protodeboronation of arylboronic acids: a higher yield of biaryls at higher temperature implies $Ea_h > Ea_{p1}, Ea_{p2}$.

on the basis of mass balances. For example, if c_A , c_B , c_C and c_D are the mole concentrations of **1–4**, respectively, then the yield of biphenyl Y_B is defined as $Y_B = [2c_B/(c_A + 2c_B + c_C + c_D)]$.

3. Results and discussion

First, the influence of the water/2-propanol ratio was studied. In the literature, the solvents used for Pd-catalyzed homocouplings of arylboronic acids are typically organic solvents or water/organic solvent mixtures in a 1:1 volume ratio. In order to optimize the reaction conditions, five experiments were carried out with water/2-propanol volume ratios of 9:1, 7:3, 5:5, 3:7 and 1:9, respectively. The results are shown in entries 1–5 of Table 1. The conversion of **1** decreased gradually from 100% to 19%, when the solvent fraction of 2-propanol was increased from 10% to 90%. In parallel, the yield of **2** also decreased from 93% to 16%. These results clearly indicate that a higher fraction of the organic solvent reduces the reaction rate, thus lowering the yield of the desired product. However, the overall yields of **3** and **4** increased slightly, relative to the yield of **2**, with increasing concentration of 2-propanol. This indicates

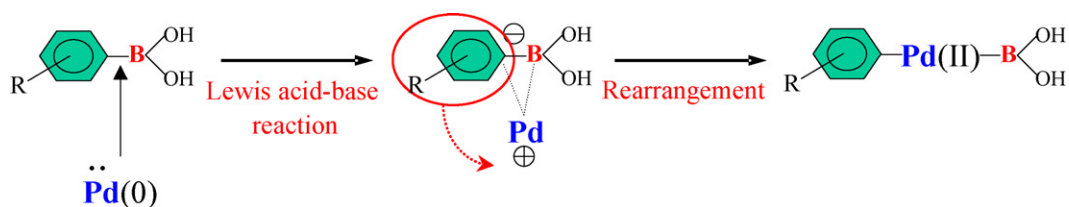
that side reactions are enhanced at higher 2-propanol fractions, consistent with the finding of Miyaura and Suzuki [17] that “the protodeboronation of 1-alkenylboronic compounds in alcohols is faster than in water.” Moreover, the reaction was carried out in pure water. The results are reported in entry 6 of Table 1 and show that both yield and selectivity are excellent even in pure water. However, due to solubility limitations of the arylboronic acids containing hydrophobic functional groups, a certain solvent fraction of 2-propanol may be necessary in an industrial implementation. In summary, we recommend that the Pd/C-catalyzed homocoupling of arylboronic acids should be carried out with a water/2-propanol volume ratio of 9:1, since under these conditions both the yield and selectivity were excellent, while allowing for sufficient solubility of the reagents.

The reaction temperature is another important factor. Smith et al. [7] studied the homocoupling of arylboronic acids catalyzed by Pd(OAc)₂ and observed an increased contribution from protodeboronation, when they carried out the reaction at higher temperatures (80 °C). On the basis of their work, we conjectured that higher yields of **2** should be obtained at lower temperatures. To test this hypothesis, five reaction runs were carried out at

Table 2
Base- and ligand-free Pd/C-catalyzed homocoupling of substituted arylboronic acids^a

Entry	Reactant	Conversion (%)	Product	Yield (%)
1		100		93
2		100		95
3		100		96
4		90		80
5		29		18
6		100		95

^a Reaction conditions: 0.64 mmol arylboronic acid, 4.6 mole% Pd/C, 10 mL water/2-propanol (9:1 volume ratio) at 75 °C under air for 3 h.



Scheme 3. Proposed mechanism for the oxidative addition of Pd(0) to arylboronic acid. The step can be divided into two sub-steps, i.e., a Lewis acid–base complexation reaction followed by rearrangement.

different temperatures (85, 65, 55, 45 °C and RT). The results are shown in entries 7–11 of Table 1. After 3 h almost complete conversion was obtained for temperatures higher than 55 °C. However, at 55 °C, the yield of **2** decreased from 93% to 88%. At the same time, the total yield of **3** and **4** increased from 7% to 12%. The higher yield of side products at lower temperatures contrasts the observations by Smith et al. [7]. The increased rate of byproduct formation at lower temperatures indicates that protodeboronation of arylboronic acids has a lower activation energy than the homocoupling reaction (Scheme 2). By considering both the yield of desired biaryls and the reaction kinetics (conversion rate), 75 °C seems to be the optimal temperature for the homocoupling reaction in our system.

Subsequently, we examined the influence of catalyst loading on the homocoupling reaction. Two experiments were carried out at 75 °C, where the Pd/C loading of 4.6 mole% was doubled or halved, respectively (entries 13 and 14 in Table 1). The reaction reached completion within 1 h at the higher catalyst loading of 9.2 mole% and gave similar product yields. The reduced catalyst loading of 2.3 mole% resulted, as expected, in a lower reaction rate and a lesser conversion (compared to the model reaction after 2 h, Fig. 1). However, it is noteworthy that the reduced catalyst loading resulted in a faster protodeboronation (higher overall yield of side products). This may imply that protodeboronation is not a catalytic reaction, competing with the catalytic homocoupling.

Recently, Yamamoto et al. [12] studied the Pd(II)-catalyzed carbonylation of arylboronic acid esters. They observed that arylboronic acids can undergo homocoupling by Pd(OAc)₂ under base- and ligand-free conditions; for example, 5 mole% Pd(OAc)₂ in methanol at RT under air with reagent **1** afforded **2** in a 99% yield after 5 h. The excellent yield motivated us to test whether our system could be improved by the use of Pd(OAc)₂. A model reaction was carried out with 4.6 mole% Pd(OAc)₂ in water/2-propanol (9:1 volume ratio) at 75 °C under air (entry 15 in Table 1). The conversion after 3 h was only 47%, which

illustrates how strongly dependent the homocoupling reaction of arylboronic acids is on the selection of the solvent.

In order to establish the versatility of our method, homocoupling of five *meta*- or *para*-substituted arylboronic acids was examined. The results are summarized in Table 2. Good to excellent yields of the desired products were obtained for arylboronic acids containing both electron donating (*m*- and *p*-Me-, *p*-MeO-) and electron withdrawing groups (*p*-Cl-). However, incorporation of the methylthio group (*p*-MeS-) resulted in a very low yield (entry 5, Table 2).

In order to further explore the influence of functional groups on reaction performance and mechanism, we modeled the Pd–arylboronic acid system using computational electronic structure methods implemented in the Gaussian 03 software package [20]. The first reaction step in the catalytic cycle proposed by Moreno-Manas et al. [2] for homocoupling of arylboronic acids is oxidative addition of Pd to the arylboronic acid. This step can be further divided into two sub-steps (Scheme 3): a Lewis acid–base complexation reaction followed by rearrangement (Pd insertion into the C–B bond). Geometry optimization (B3LYP/SDD/6-31 + G(d,p) with PCM water solvation model) showed that the electron-rich Pd(0) atom coordinates with no activation barrier to the phenyl ring of the arylboronic acids, not to the B atom [2]. The Pd(0) atom preferentially interacts with the phenyl π -system and is located symmetrically between *ipso* and *ortho* C atoms (C–Pd \sim 2.16 Å, B–Pd \sim 2.79 Å), Fig. 2. No minimum could be found in which Pd(0) coordinated with the B atom; all such initial trial structures rearranged upon energy minimization to the phenylic π -complex without crossing an activation barrier. The LUMO of boronic acid is a phenylic π^* -orbital with some contribution from the B atom, and strong π -donation from the OH groups probably renders the B center a weaker electron acceptor (acid) than the phenyl π -system. The computed free energies of complex formation are shown in Table 3. They are all favorably negative (\sim –110 kJ/mole) without much variation among the various substituents. We conclude,

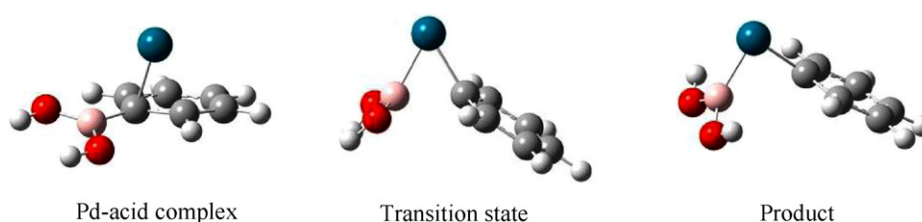
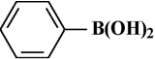
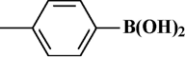
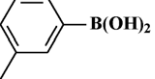
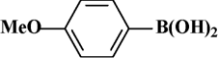
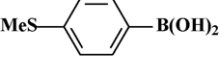
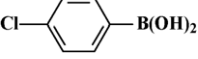


Fig. 2. Optimal geometries of Pd-boronic acid complex, transition state for Pd insertion into the C–B bond, and the insertion (rearrangement) product.

Table 3
Computed free energy differences (B3LYP/SDD/6-31+G(d,p) and PCM water solvation model) for species involved in the oxidative addition of Pd(0) to boronic acid (Fig. 2).

Boronic acid	ΔG (complex) ^a	ΔG^\ddagger (insert.) ^b	ΔG (product) ^a
	-109.0	57.9	-79.8
	-103.3	54.6	-70.4
	-108.1	51.4	-76.4
	-115.5	53.7	-84.3
	-104.7	58.3	-71.5
	-107.2	60.1	-75.5

^a Free energy differences are in kJ/mole and relative to the energies of separated reactants (one Pd atom plus one boronic acid molecule). The free energy differences were computed using a reference state of 1 M concentration for each species participating in the reaction, and $T = 298.15$ K.

^b Activation free energy (kJ/mole) measured relative to complex.

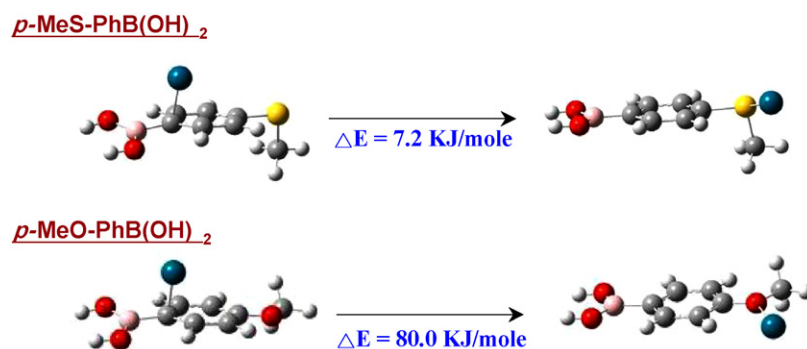
in agreement with Moreno-Manas et al. [2] that the initial step of the homocoupling reaction (complex intermediate formation, Scheme 3) is fast and, furthermore, not particularly sensitive to substituents on the aryl group.

However, the reactivity of the different arylboronic acids might depend on the second step, the rearrangement of the R-Ph group. Although, the rearrangement step is endothermic, the computed enthalpies fall in a narrow range (30–35 kJ/mole), which suggests small activation energy differences between different Pd-arylborenic acid pairs. The modest and quite similar activation energies actually computed (Table 3) indicate that the insertion step should be facile at ambient temperatures. However, the computed activation energies do not provide a reason for the poor performance of the *p*-MeS boronic acid.

A plausible explanation for the low yield observed during the homocoupling of *p*-MeS-Ph-B(OH)₂ may be found in the strong affinity shown by sulfur for palladium [21], which could result in poisoning of the active palladium sites. To test this

hypothesis, a model reaction (entry 1 in Table 1) was carried out in the presence of *p*-MeS-Ph-B(OH)₂ (5 mole%). The conversion of **1** and the yield of **2** after 3 h were 99% and 89%, respectively. The high conversion indicates that the Pd catalyst was not poisoned by sulfur. Also, a new biaryl, i.e., MeS-Ph-Ph (~2% yield), was observed. Thus, we conclude that sulfur does not poison the palladium sites.

DFT calculations were carried out focusing on a comparison of Pd complexes formed with *p*-MeS-Ph-B(OH)₂ and *p*-MeO-Ph-B(OH)₂. A complex in which Pd(0) bonded to the S atom of *p*-MeS-Ph-B(OH)₂ was found to be only 7.2 kJ/mole higher in energy than the phenylic π -complex discussed above (Scheme 4). Thus, the calculations suggest that sulfur does not irreversibly bind to Pd. However, the small energy difference computed between the two types of complexes suggests that both (Pd-S and Pd-phenyl) may form at comparable rates, thus reducing catalyst activity. In contrast, for the corresponding Pd(0) complex with *p*-MeO-Ph-B(OH)₂ acid a much larger



Scheme 4. Energy comparisons of Pd(0) complexes formed with *p*-MeS-PhB(OH)₂ and *p*-MeO-PhB(OH)₂. The small energy difference between the two *p*-MeS-PhB(OH)₂ complexes suggests that sulfur may interfere with the activity of Pd.

energy difference of 80.0 kJ/mole was computed (Pd–O versus Pd–phenyl).

4. Conclusions

In summary, we have developed a base- and ligand-free catalytic system to synthesize symmetrical biaryls by homocoupling of arylboronic acids. Under optimal conditions, i.e., about 4.6 mole% Pd/C in water/2-propanol (9:1 volume ratio) at 75 °C under air, excellent yields of the desired products can be obtained after 3 h for phenylboronic acid derivatives containing electron-donating and electron-withdrawing groups. However, a *p*-MeS substituent resulted in extremely low yields. DFT calculations indicate that the presence of sulfur in the functional group reduces catalyst activity by competing for the active metal site. Furthermore, the calculations suggest that the reactivity of different arylboronic acids may be relatively independent of the first step in the homocoupling reaction, oxidative addition of Pd to the arylboronic acid.

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