PAPER

Oxygen-promoted PdCl₂-catalyzed ligand-free Suzuki reaction in aqueous media†

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A simple and efficient protocol has been developed for the PdCl₂-catalyzed ligand-free and aerobic Suzuki reaction of aryl bromides or nitrogen-based heteroaryl bromides with arylboronic acids in good to excellent yields in aqueous ethanol. A systematic investigation on the effect of different atmospheres on the reactivity of the palladium-catalyzed Suzuki reaction has been carried out, the results show that an aerobic atmosphere demonstrates a positive effect on the reactivity of the Suzuki reaction in an aqueous media and a negative effect in a pure organic solvent, which exhibits that the water plays a crucial role for the function of the atmosphere on the palladium-catalyzed ligand-free Suzuki reaction.

Introduction

Palladium-catalyzed cross-coupling reactions have been recognized as powerful tools for the carbon–carbon bond formation and have been widely used in the synthesis of natural products, pharmaceuticals and advanced functional materials.[1] Over the past decade, sterically demanding and electron-rich ligands have been developed for highly effective Suzuki reactions.[2] Due to the water- and/or air-sensitivity of most ligands, numerous efforts and advances have been made to solve these problems, including designing oxygen and/or moisture-stable ligands *via* multi-step synthesis[3] or supporting the ligand on functional supports.[4] Among the recent achievements on this topic, the development of "ligand-free" catalytic systems has been one of the most challenging fields in synthetic organic chemistry, because they are the simplest and cheapest systems in comparison to the ligand-promoted ones.[5] More importantly, the "ligand-free" catalytic system makes it possible to carry out the Suzuki reaction under an aerobic atmosphere and/or in an aqueous media. Recently, different aerobic ligand-free aqueous catalytic systems have been reported to perform the Suzuki reaction at room temperature, for example, Pd/C in aqueous ethanol,[6] Pd(OAc)₂ in aqueous acetone,[7] and Pd(OAc)₂ in aqueous ethylene glycol monomethyl ether.[8]

However, there are still open-questions in the aerobic ligand-free aqueous protocols for the Suzuki reaction. One of them is the effect of the atmosphere on such a transformation. In 2003, Jung *et al.* observed a negative effect of oxygen on the Pd(OAc)₂-catalyzed ligand-free Suzuki reaction in DMF.[9] Later, Sajiki *et al.*[6] reported the effects of the inert and aerobic atmospheres on the Pd/C-catalyzed ligand-free aqueous Suzuki reaction. Their results showed that the atmospheres did not influence the cross-coupling process. We recently noticed that the Suzuki reaction of aryl chlorides catalyzed by the *in situ*-generated palladium nanoparticles was promoted by the oxygen in PEG-400 at room temperature.[10] Very recently, we found that the oxygen could promote the Suzuki reaction of 2-pyridyl bromides in aqueous isopropanol.[11] Therefore, the influence of the atmosphere on the palladium-catalyzed Suzuki reaction has not been fully investigated. Herein, we report an oxygen-promoted cross-coupling reaction catalyzed by palladium(II) salts in aqueous ethanol at room temperature and the successful application of this protocol to the Suzuki reaction of nitrogen-based heteroaryl bromides. Noticeably, an overall investigation of the effects of different atmospheres on the Suzuki reaction in both aqueous medium and pure organic solvents is described.
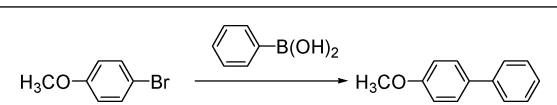
Results and discussion

Optimization of reaction conditions

In our concept, the zero-valent palladium, the catalyst in the reaction, is generated *in situ* from palladium(II) salts in the reaction system. Therefore, we first tested the effects of different precatalysts on the model cross-coupling of 4-bromoanisole with phenylboronic acid in 50% aqueous ethanol under air at room temperature. The results are illustrated in Table 1. It was clear that precatalysts with palladium(II) salts such as Pd(OAc)₂ and PdCl₂ exhibited high catalytic activity. Using 0.5 mol% PdCl₂, the cross-coupling reaction could give the cross-coupling product quantitatively in 30 min (Table 1, entry 2). However, no reaction occurred when zerovalent palladium sources such as Pd₂(dba)₃ or Pd/C were used (Table 1, entries 3 and 4), which was consistent with both our recent results[10] and Li's report.[5h] Interestingly,

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Table 1 Effects of precatalysts on the Suzuki reaction of 4-bromoanisole with phenylboronic acid[a]

H₃CO—⟨benzene⟩—Br + ⟨benzene⟩—B(OH)₂ → H₃CO—⟨benzene⟩—⟨benzene⟩

Entry	Precatalysts	Isolated yield (%)
1	Pd(OAc)₂	91
2	PdCl₂	100
3	Pd₂(dba)₃	No reaction
4	Pd/C (5%)	No reaction
5	PdO	Trace
6	PdCl₂	68[b]
7	PdCl₂	Trace[c]

[a] Reaction conditions: 4-bromoanisole (0.5 mmol), phenylboronic acid (0.75 mmol), palladium loading (0.5 mol%), Base (1.0 mmol), reaction time: 30 min, 50% EtOH (4 mL), 25 °C, in air. [b] 2 mol% TPPTS was used in air. [c] 2 mol% TPPTS was used in nitrogen.

Table 2 Effects of atmospheres on the reaction of aryl bromides with phenylboronic acid in 50% EtOH[a]

| Entry	Aryl bromides	Atmospheres	Isolated yield (%)
1	4-Bromoanisole	Open air	100
2	4-Bromoanisole	O₂ balloon	100
3	4-Bromoanisole	N₂	72
4	4-Bromoanisole	H₂ balloon	49
5	4-Bromoanisole	CO₂ balloon	12
6	4-Bromoanisole	CO balloon	No reaction
7	2-Bromoanisole	Open air	87
8	2-Bromoanisole	O₂ balloon	89
9	2-Bromoanisole	N₂	32
10	2-Bromoanisole	H₂ balloon	26
11	2-Bromoanisole	CO₂ balloon	11
12	2-Bromoanisole	CO balloon	No reaction

[a] Reaction conditions: bromoanisole (0.5 mmol), phenylboronic acid (0.75 mmol), PdCl₂ (0.5 mol%), K₂CO₃ (1.0 mmol), 30 min, 25 °C.

adding a water-soluble ligand TPPTS decreased the catalytic activity. In open air, PdCl₂-TPPTS gave a 68% isolated yield (Table 1, entry 6) and little product was obtained when the reaction was carried out under nitrogen (Table 1, entry 7). The reason for this might be that the palladium-TPPTS complex needed a long induction period to be activated under nitrogen, while the reaction performed in open air, a partial amount of TPPTS was oxidized and the coordination ability was reduced. Also the cross-coupling product was trace when using PdO as a catalyst (Table 1, entry 5). We suppose that it is difficult to transfer Pd(II) to Pd(0) from PdO in aqueous media.

As reported in Table 2, we next studied the impacts of different atmospheres, namely, open air, oxygen, nitrogen, hydrogen, carbon monoxide, and carbon dioxide, on the cross-couplings of 4-bromoanisole and 2-bromoanisole with phenylboronic acid using 0.5 mol% PdCl₂ as a precatalyst at 25 °C, respectively. The same as our recently published results, both of the cross-couplings favored an aerobic atmosphere. In case of 4-bromoanisole, the cross-coupling reaction reached quantitatively in 30 min in both open air and oxygen (Table 2, entries 1 and 2); 72% isolated yield in nitrogen (Table 2, entry 3); 49% in hydrogen (Table 2, entry 4); 12% in CO₂ (Table 2, entry 5), and no reaction occurred in CO (Table 2, entry 6).

The reaction of 2-bromoanisole with phenylboronic acid gave nearly the same results except a little decrease in reactivity because of the steric effect (Table 2, entries 7–12). As known that the air is composed mainly of nitrogen (78%) and oxygen (21%), the results in Table 2 show clearly that an aerobic atmosphere is necessary for a fast transformation.

The kinetic studies were performed on the Suzuki reaction of 4-bromoanisole with phenylboronic acid under air or N₂, respectively. The results are illustrated in Fig. 1. It is clear that the reaction proceeded rather slowly and the induction period was apparent in nitrogen. While the cross-coupling under air resulted in the absence of the induction period and a sharp increase in the initial rate. For example, 82% isolated yield was obtained within 10 min under air, which was much higher than that in nitrogen in the same reaction time. Therefore, a conclusion can be drawn that it is the oxygen that shortens the induction period and promotes the Suzuki reaction in the ligand-free 50% aqueous ethanol system.
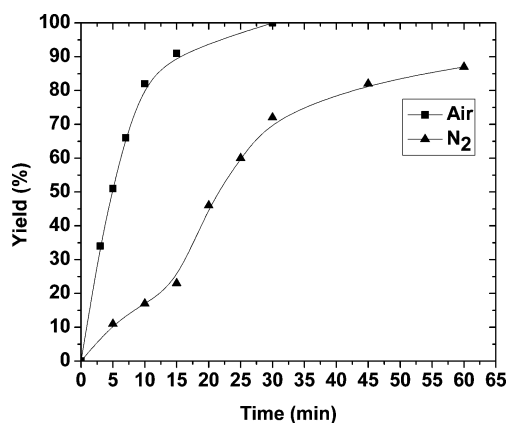
Fig. 1 Yield *vs.* time curves of the Suzuki reaction of 4-bromoanisole with phenylboronic acid in 50% EtOH under air or nitrogen.

To further investigate the generality of oxygen-promoted ligand-free Suzuki reaction, we examined the effect of nitrogen or air on the Suzuki reaction of 4-bromoanisole with phenylboronic acid in different solvents. The results are illustrated in Table 3. Gratifyingly, we observed that the couplings gave higher yields under air than in nitrogen in aqueous medium. (Table 3, entries 1a–5a *vs.* 1b–5b). For example, in 50% aqueous acetone, the reaction resulted in 82%, 75% and 67% isolated yields in oxygen, air and nitrogen, respectively (Table 3, entry 1c, 1a and 1b). However, when the reaction proceeded in pure organic solvent, the reaction rate was much slower than that in aqueous media. Moreover, it was noteworthy that the reactivity was much lower under air than in nitrogen in pure organic solvents (Table 3, entries 6a–11a *vs.* 6b–11b). The results in pure organic solvents were consistent with Jung's report.[9] For instance, in pure ethanol, the reaction afforded 4-methoxybiphenyl in 54% and 83% yields in air and nitrogen, respectively (Table 3, entry 6a *vs.* 6b), while 100% and 72% isolated yields were obtained for the same reaction in air and in nitrogen, respectively, in 50% aqueous ethanol (Table 2, entry 1 *vs.* 3). The results disclosed that the water played a crucial role in the influence of the atmosphere on the palladium-catalyzed ligand-free Suzuki reaction. After adding a suitable amount of water, the oxygen-inhibited Suzuki reaction in pure organic solvent was switched to the oxygen-promoted system in aqueous media.

Table 3 Effects of atmospheres on the Suzuki reaction of 4-bromoanisole and phenylboronic acid in different solvents[a]

Entry	Solvent	Atmosphere	PdCl$_2$ (%)	Time/min	Isolated yield (%)
1a	Acetone/H$_2$O	Air	0.5	10	75[b]
1b		Nitrogen			67[b]
1c		O$_2$ balloon			82[b]
2a	DMF–H$_2$O	Air	0.5	5	99[b]
2b		Nitrogen			83[b]
3a	i-PrOH/H$_2$O	Air	0.5	10	93[b]
3b		Nitrogen			49[b]
4a	i-Butanol/H$_2$O	Air	0.5	60	14[b]
4b		Nitrogen			4[b]
5a	THF–H$_2$O	Air	0.5	120	63[b]
5b		Nitrogen			39[b]
6a	Ethanol	Air	0.5	17	54
6b		Nitrogen			83
7a	i-PrOH	Air	0.5	30	9
7b		Nitrogen			20
8a	Acetone	Air	0.5	120	24
8b		Nitrogen			35
9a	DMF	Air	1	120	Trace
9b		Nitrogen			55
10a	THF	Air	1	120	12
10b		Nitrogen			23
11a	i-Butanol	Air	1	120	8
11b		Nitrogen			42

[a] Reaction conditions: 4-bromoanisole(0.5 mmol), phenylboronic acid (0.75 mmol), PdCl$_2$ (0.5–1 mol%), K$_2$CO$_3$ (1.0 mmol), solvent (4 mL), 25 °C. [b] Co-sovent/H$_2$O (v/v = 1/1)

As literature described,[12] the volume ratio between organic solvent and water could affect the rate of the cross-coupling reaction.[7] Therefore, we next studied the effects of the ratio of ethanol to water on the Suzuki reaction of 4-bromoanisole with phenylboronic acid. The reactions were carried out using K$_2$CO$_3$ as base in the presence of 0.5 mol% PdCl$_2$ at 25 °C in air (see ESI†). Initially, we tried to proceed the reaction in pure water, but only a trace of the product was obtained. When the ratio of ethanol to water was 1 : 2, the reaction still afforded 4-methoxybiphenyl in a low yield of 37% in 30 min. However, the reactivity enhanced rapidly with the addition of an incremental amount of ethanol, and a quantitative isolated yield was obtained when the volume ratio of ethanol and water was 1 : 1. While further increasing the amount of ethanol, the isolated yield of the cross-coupling product decreased a little. The results showed that the ratio of ethanol to water played a key role in the ligand-free Suzuki reaction. We deduced that a suitable amount of water in the reaction mixture could shorten the induction period and increase the initial rate.[13]
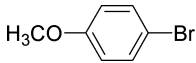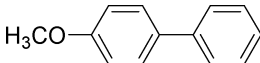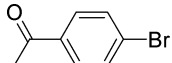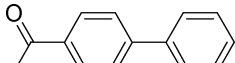
Scope and limitations of substrates
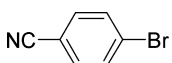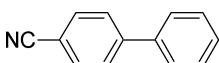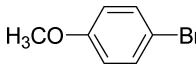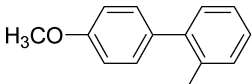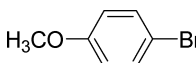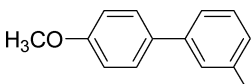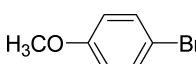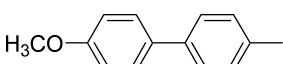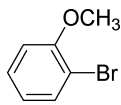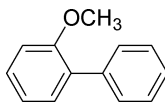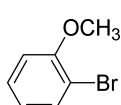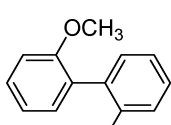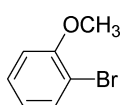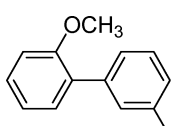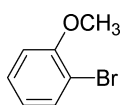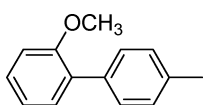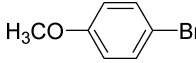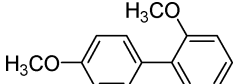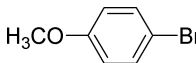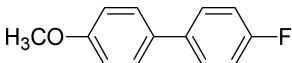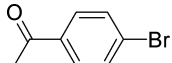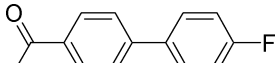
The scope and limitations of the PdCl$_2$-EtOH–H$_2$O catalytic system for deactivated aryl bromides with various arylboronic acids were investigated in open air at 25 °C. The results in Table 4 exhibited that the Suzuki reaction between 4-bromoanisole and tolylboronic acids gave a quantitative yield in the presence of 0.5 mol% PdCl$_2$ as catalyst (Table 4, entries 4, 5 and 6). The cross-coupling reaction proceeded also very fast even increasing the steric effect of aryl bromide or arylboronic acid (Table 4, entries 7, 9–11). However, increasing the steric effect in both aryl bromide and arylboronic acid could decrease the reactivity of the cross-coupling, a 61% isolated yield was obtained in 6 h between 2-bromoanisole and 2-tolylboronic acid (Table 4, entry
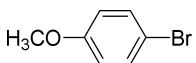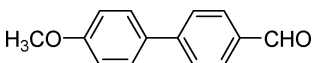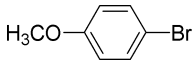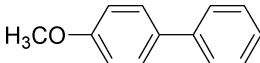
8). To further investigate the catalytic activity of the PdCl$_2$-EtOH–H$_2$O system, we chose the arylboronic acids containing electron-neutral or electron-withdrawing group as coupling partners, which provided the products in 99% and 52% isolated yields using 4-flurophenylboronic acid and 4-formylphenylboronic acid, respectively (Table 4, entries 12 and 14). These results show that the stronger the electron-donating group in arylboronic acid is, the higher the catalytic activity is. This is because an electron-rich arylboronic acid could accelerate the rate of the transmetalation step in the Suzuki reaction.
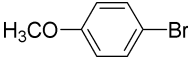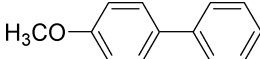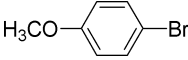
We further reduced the palladium loading down to 0.2 mol% and 0.1 mol% to test the efficiency of the catalytic system, the cross-couplings between 4-bromoanisole and phenylboronic acid were completed quantitatively in 35 min and 40 min, respectively (Table 4, entries 15 and 16), resulting in the highest TOF up to 1500 h^{-1} (Table 4, entry 16). Interestingly, 70% isolated yield of 4-methoxybiaryl was obtained without stirring for 24 h at 25 °C, which further demonstrated that the PdCl$_2$-ethanol (50%) system was highly efficient (Table 4, entry 17).
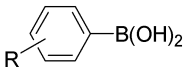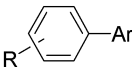
The Suzuki reaction involving heterocycles is of great interest to the pharmaceutical industry because of the special biological activities displayed by the heterobiaryl compounds. However, it is reported that heteroaryl halides show a slower reaction rate and are unsuitable coupling partners in the Suzuki reaction, due to the potential binding nature of such substrates to the metal center resulting in the formation of inactive substrate-metal complexes.[14] Recently, ligand-free protocols for the synthesis of heterobiaryls containing a 2-pyridyl moiety have emerged.[5d,15] Unfortunately, the ligand-free Suzuki reaction usually encounters with a low reactivity against 2-halopyridines. In this regard, the best was Sajiki et al.[5d] who reached quantitative formation of 2-phenylpyridine using 3.5 mol% Pd/C (10%) in 50% isopropanol at 80 °C for 24 h under argon. Very recently, we reported a

Table 4 The Suzuki reaction of aryl bromides with arylboronic acids[a]

$$\text{Ar-Br} \quad + \quad \underset{R}{\bigcirc}\text{-B(OH)}_2 \quad \xrightarrow[\text{50\% EtOH, rt}]{\text{0.5 mol\% PdCl}_2} \quad \underset{R}{\bigcirc}\text{-Ar}$$

Entry	Ar–Br	R	Product	Time/min	Isolated yield (%)
1	H$_3$CO–⟨⟩–Br	H	H$_3$CO–⟨⟩–⟨⟩	25	100
2	O=C(CH$_3$)–⟨⟩–Br	H	O=C(CH$_3$)–⟨⟩–⟨⟩	10	99
3	NC–⟨⟩–Br	H	NC–⟨⟩–⟨⟩	8	99
4	H$_3$CO–⟨⟩–Br	2-CH$_3$	H$_3$CO–⟨⟩–⟨⟩CH$_3$	15	98
5	H$_3$CO–⟨⟩–Br	3-CH$_3$	H$_3$CO–⟨⟩–⟨⟩CH$_3$	15	99
6	H$_3$CO–⟨⟩–Br	4-CH$_3$	H$_3$CO–⟨⟩–⟨⟩–CH$_3$	10	100
7	OCH$_3$, ⟨⟩–Br	H	OCH$_3$, ⟨⟩–⟨⟩	40	95
8	OCH$_3$, ⟨⟩–Br	2-CH$_3$	OCH$_3$, ⟨⟩–⟨⟩CH$_3$	360	61
9	OCH$_3$, ⟨⟩–Br	3-CH$_3$	OCH$_3$, ⟨⟩–⟨⟩CH$_3$	15	99
10	OCH$_3$, ⟨⟩–Br	4-CH$_3$	OCH$_3$, ⟨⟩–⟨⟩–CH$_3$	15	100
11	H$_3$CO–⟨⟩–Br	2-OCH$_3$	H$_3$CO–⟨⟩–⟨⟩OCH$_3$	15	99
12	H$_3$CO–⟨⟩–Br	4-F	H$_3$CO–⟨⟩–⟨⟩–F	30	99
13	O=C(CH$_3$)–⟨⟩–Br	4-F	O=C(CH$_3$)–⟨⟩–⟨⟩–F	30	98
14	H$_3$CO–⟨⟩–Br	4-CHO	H$_3$CO–⟨⟩–⟨⟩–CHO	45	52
15	H$_3$CO–⟨⟩–Br	H	H$_3$CO–⟨⟩–⟨⟩	35	99[b]

Table 4 (Contd.)

Ar-Br + R—⟨ ⟩—B(OH)₂ →(0.5 mol% PdCl₂ / 50% EtOH, rt)→ R—⟨ ⟩—Ar

Entry	Ar–Br	R	Product	Time/min	Isolated yield (%)
16	H₃CO—⟨ ⟩—Br	H	H₃CO—⟨ ⟩—⟨ ⟩	40	99[c]
17	H₃CO—⟨ ⟩—Br	H	H₃CO—⟨ ⟩—⟨ ⟩	24 h	70[d]

[a] Reaction conditions: aryl bromides (0.5 mmol), arylboronic acids (0.75 mmol), PdCl₂ (0.5 mol%), K₂CO₃ (1.5 mmol), 50% EtOH (4 mL), 25 °C, in air. [b] The PdCl₂ loading was 0.2 mol%. [c] The PdCl₂ loading was 0.1 mol%. [d] The PdCl₂ loading was 0.5 mol%, without stirring.

Table 5 The Suzuki reaction of 2-bromopyridine with arylboronic acids[a]

⟨pyridine⟩—Br + R—⟨ ⟩—B(OH)₂ ⟶ ⟨pyridine⟩—⟨ ⟩—R

Entry	R	Time/min	Isolated yield (%)
1	4-CH₃	480	40[b]
2	H	150	82[c]
3	H	100	29[d]
4	H	100	98
5	H	100	41[e]

[a] Reaction conditions: 2-bromopyridine (0.5 mmol), arylboronic acids (0.75 mmol), PdCl₂ (1.5 mol%), K₃PO₄·7H₂O (1.5 mmol), 50% EtOH (4 mL), 80 °C, in air. [b] The PdCl₂ loading was 1.0 mol%, and the reaction proceeded at 25 °C. [c] 1.5 mmol K₂CO₃ was used. [d] 1.5 mmol NaOH was used. [e] The reaction proceeded in N₂ atmosphere.

fast protocol for the ligand-free Suzuki reaction of 2-halogenated pyridines in 50% aqueous isopropanol. A 96% isolated yield of 2-phenylpyridine was obtained in the presence of 1.5 mol% Pd(OAc)₂ at 80 °C for 30 min in air.[11] Considering the high catalytic activity of PdCl₂-ethanol (50%) system, we also attempted to extend this system to the synthesis of 2-aryl-substituted pyridyl derivatives, and the results are summarized in Table 5. Using 1 mol% PdCl₂ as catalyst, the Suzuki coupling between 2-bromopyridine and 4-tolylboronic acid only gave the coupling product in 40% isolated yield after 8 h at 25 °C (Table 5, entry 1). However, the reactivity of 2-bromopyridine with phenylboronic acid enhanced dramatically using 1.5 mol% PdCl₂ as catalyst in 150 min at 80 °C and gave 82% isolated yield (Table 5, entry 2). When other bases such as NaOH and K₃PO₄·7H₂O were tested under the above conditions, we found that the coupling could be completed in 100 min when using K₃PO₄·7H₂O (Table 5, entry 4). While it only provided 2-phenylpyridine in 41% isolated yield under N₂ (Table 5, entry 5), which further demonstrated the promotion of O₂ on the Suzuki reaction in the PdCl₂-50% ethanol system. In comparison to Sajiki's[6] and Pan's[5e] reports, the PdCl₂-ethanol (50%) system manifested higher catalytic activity.

Under the optimized conditions, the scope of the reactions using 2-bromopyridine and arylboronic acids was investigated. The results are summarized in Table 6. The reactions of 2-bromopyridine with a series of 4-substituted arylboronic acids provided the desired heterobiaryl products with more than 90%

isolated yields (Table 6, entries 2, 3, 5 and 6). While increasing the steric hindrance of arylboronic acids, the reactivity decreased and gave 67% and 55% corresponding coupling products in 300 min when 2-tolylboronic acid or 2-methoxyl phenylboronic acid was used, respectively (Table 6, entries 1 and 4). It was worth noting that the reaction between 2-bromopyridine and 4-tolylboronic acid could be completed in 10 min (Table 6, entry 3), even after reducing the loading of PdCl₂ to 0.5 mol%, the reaction gave 93% isolated yield in 70 min (Table 6, entry 7). The couplings of 5-bromopyrimidine with phenylboronic acid or 4-tolylboronic acid gave nearly quantitative yields in 60 min and 40 min, respectively (Table 6, entries 8 and 9). Moreover, 80% 4-tolylpyrimidine was obtained in 150 min when 0.5 mol% PdCl₂ was used (Table 6, entry 10).
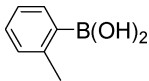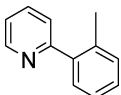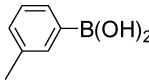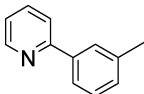
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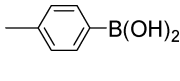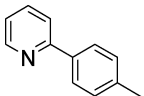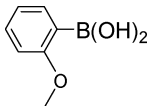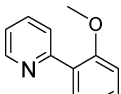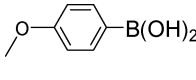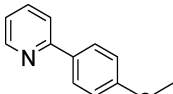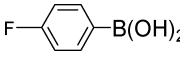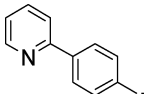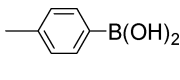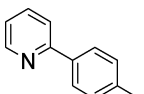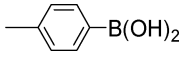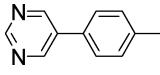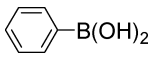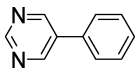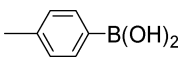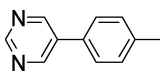
In summary, we have developed a simple, efficient and ligand-free protocol for the Suzuki reaction of aryl bromides or N-hetroaryl bromides with arylboronic acids catalyzed by the Pd(II) salts in 50% ethanol. It was noteworthy that the presence of water could reverse the role of atmospheres on the palladium-catalyzed ligand-free Suzuki reaction, converting the oxygen-inhibited system in pure organic solvent into the oxygen-promoted protocol in aqueous media. Furthermore, this aerobic and water-involved protocol is in accordance with the concept of green chemistry and of great interest for practical production. The nature of the oxygen and water in this type of transformation and the applications of the catalytic system to other transformations are currently under investigation in our laboratory.

Experimental section

General remarks

Unless otherwise noted, all the reactions were carried out under air. All aryl halides and arylboronic acids were purchased from Alfa Aesar, Avocado and used without purification. ¹H NMR spectra were recorded on a Varian Inova 400 spectrometer. Chemical shifts are reported in ppm relative to TMS. Mass spectroscopy data of the product were collected on a MS-EI instrument. All products were isolated by short chromatography on a silica gel (200–300 mesh) column using petroleum ether

Table 6 The Suzuki reaction of *N*-heteroaryl bromides with arylboronic acids[a]

Entry	Ar–B(OH)₂	Product	Time/min	Yield (%)[b]
1			300	67
2			20	99
3			10	99
4			300	55
5			20	99
6			25	95
7			70	93[c]
8			60	93
9			40	98
10			150	80[c]

[a] Reaction conditions: heteroaryl bromides (0.5 mmol), arylboronic acids (0.75 mmol), PdCl₂ (1.5 mol%), K₃PO₄·7H₂O (1.5 mmol), 50% EtOH (4 mL), 80 °C, in air. [b] Isolated yield. [c] PdCl₂ 0.5 mol%.

(60–90 °C), unless otherwise noted. Compounds described in the literature were characterized by ¹H NMR spectra to reported data.

Typical experimental procedure for the Suzuki reaction of aryl bromides with arylboronic acids

A mixture of aryl bromide (0.5 mmol), arylboronic acid (0.75 mmol), PdCl₂ (0.5 mol%), K₂CO₃ (1 mmol), distilled water (2 mL) and EtOH (2 mL) was stirred at room temperature under air for the indicated time. The mixture was added to brine (15 mL) and extracted four times with diethyl ether (4 × 15 mL). The

solvent was concentrated under vacuum and the product was isolated by short chromatography on a silica gel (200–300 mesh) column.

Acknowledgements

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