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Article

Pd/C-catalyzed ligand-free and aerobic Suzuki reaction in water

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ABSTRACT

A general and efficient catalytic system for Pd/C-catalyzed ligand-free aerobic Suzuki cross-coupling reactions was developed. The reaction tolerated a wide range of aryl bromides with a hydrophilic group or a hydrophobic group without any additives in water. Moreover, the catalytic system was successfully extended to the cross-couplings of heteroaryl halides with various arylboronic acids. The Pd/C catalyst could be reused three times without significant loss of catalytic activity.

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1. Introduction

The need for sustainable development in the 21st century is employing new technologies and efficient processes for solving many environmental problems, and is gaining increasing importance in the chemical industry [1–4]. So far, much effort has been made to improve the efficiencies of organic reactions using standard synthetic operations. Most research has focused on homogeneous catalysis, which provides excellent activity and selectivity, however, it has a number of drawbacks, mainly associated with the recovery and reuse of the catalyst. Heterogeneous catalysis provides a possible solution to these problems [5,6]. Pd on activated charcoal (Pd/C), a widely used heterogeneous catalyst for hydrogenation, has been used for various transformations, including C–C, C–N, and C–O bond formations, because of its easy access and low cost [7]. The Pd-catalyzed Suzuki reaction is one of the most versatile and

powerful tools for C–C bond formation in the synthesis of biaryl compounds, the skeletons of which are found in a wide range of important compounds, including pharmaceuticals, natural products, and advanced functional materials [8–10].

The solvent is a key parameter in the Suzuki reaction. Water has many advantages over common organic solvents: abundant, cheap, non-toxic, and non-flammable. The need to develop sustainable chemistry has increasingly led chemists to consider using water as a benign solvent [11,12]. As reported by Blackmond and coworkers, the use of water is only environmentally friendly if organics and metals can be fully extracted from the aqueous phase [13]. Heterogeneous catalysis using a metal sequestered on a water-insoluble support could meet these requirements because the supported catalyst can be easily removed by filtration [14,15]. In 1997, Bumagin et al. [16] reported the first example of Pd/C-catalyzed cross-coupling in water, by reacting water-soluble 3-bromobenzoic acid with

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tetraphenylborate in neat water. Later, Xu and coworkers [17] confirmed that water-soluble aryl bromides could react efficiently with NaBPh_4 and NaBtO_4 in refluxing water with a low catalyst loading. However, these methods are limited to water-soluble aryl bromides or aryl iodides. This problem can be solved by adding surfactants [18,19] or organic cosolvents [20,21] to increase the solubilities of non-water-soluble aryl halides. To the best of our knowledge, a general approach to Pd/C-catalyzed Suzuki reactions of aryl halides with a broad range of water solubilities in neat water in the absence of additives has not been reported.

Our group has a long-standing interest in developing efficient aerobic and aqueous catalytic systems for Pd-catalyzed ligand-free cross-coupling reactions, and a series of efficient and universal catalytic systems has been developed [22–25]. In this paper, we describe a recyclable catalytic system for the Pd/C-catalyzed cross-coupling of a wide range of aryl bromides with arylboronic acids, without any additives, in water.

2. Experimental

2.1. General remarks

The water used in the experiments was deionized. Aryl bromides and arylboronic acids were purchased from Alfa Aesar. Other chemicals were obtained commercially and used without purification. ^1H nuclear magnetic resonance (^1H NMR) spectra were recorded with a Bruker Avance II 400 MHz spectrometer, using tetramethylsilane (TMS) as an internal standard. All the products were isolated by short chromatography on a silica-gel (200–300 mesh) column, using petroleum ether (60–90 °C) as the eluent, unless otherwise stated. Compounds that had previously been described in the literature were characterized by comparison of their ^1H NMR spectra with the reported data.

2.2. General procedure for Suzuki reaction

An aryl halide (0.5 mmol), arylboronic acid (0.75 mmol), $(i\text{-Pr})_2\text{NH}$ (1.0 mmol), Pd/C (1.5 mol%, 16 mg), and water (1.0 mL) were allowed to react at 100 °C. After a certain period, the reaction mixture was added to brine (10 mL) and extracted with ethyl acetate (3×10 mL). The solvent was concentrated under vacuum, and the product was isolated by short chromatography on a silica-gel (200–300 mesh) column.

2.3. Recyclability tests

For the first run, a mixture of 4-bromobenzonitrile (0.5 mmol), 4-methylphenylboronic acid (0.75 mmol), $(i\text{-Pr})_2\text{NH}$ (1.0 mmol), Pd/C (1.5 mol%, 16 mg), and water (1.0 mL) was allowed to react at 100 °C for the indicated time. The system was cooled to room temperature and the reaction mixture was passed through a membrane filter (0.45 μm), and washed sequentially with ethanol (15 mL) and water (5 mL). The filter residue was naturally air dried for 24 h for the next reaction cycle. The filtrate was concentrated under vacuum, and then

added to brine (10 mL) and extracted with ethyl acetate (3×10 mL). The residue was purified by flash column chromatography on silica gel (200–300 mesh) to give the corresponding biaryl compound.

3. Results and discussion

3.1. Optimization of reaction conditions

The cross-coupling of 4-bromoanisole and phenylboronic acid in the presence of 1.5 mol% Pd/C at 100 °C in water was chosen as the model reaction. The influence of various bases on the cross-coupling reaction was investigated; the results are summarized in Table 1. Initially, a series of typical organic bases was examined (Table 1, entries 1–8). Triethylamine or diisopropylethylamine, which are often used as bases in Pd-catalyzed cross-coupling reactions [26,27], showed similar activity in the present protocol (Table 1, entries 1 and 2). Diisopropylamine and isopropylamine gave very different results (Table 1, entries 3 and 4). It is clear that diisopropylamine is the most efficient base in this catalytic system, providing 93% isolated yield of the cross-coupled product in 20 min. Tripropylamine and dipropylamine were inefficient (Table 1, entries 5 and 6), even though their structures are similar to that of diisopropylamine. The cyclic amine piperazine and 1,4-diazabicyclo[2.2.2]octane (DABCO) were also tested in this catalytic system (Table 1, entries 7 and 8). Lower yields were obtained with the organic alkali sodium methoxide (Table 1, entry 9). Common inorganic bases gave disappointing results in the present protocol (Table 1, entries 10–12), even though they are soluble in water and have been successfully used in efficient ligand-free catalytic systems [28]. In this Pd/C-catalyzed system, the reason for the high efficiency is probably that diisopropylamine acts not only as a base but also as a ligand, and has a high tendency to coordinate to Pd to form active species, as reported by Boykin et al. [26] and as suggested in our previous work [27].

Table 1

Effect of base on cross-coupling of 4-bromoanisole with phenylboronic acid.

Entry	Base	Isolated yield (%)
1	Et_3N	69
2	$(i\text{-Pr})_2\text{NEt}$	59
3	$(i\text{-Pr})_2\text{NH}$	93
4	$i\text{-PrNH}_2$	35
5	$(n\text{-Pr})_3\text{N}$	8
6	$(n\text{-Pr})_2\text{NH}$	7
7	Piperazine	7
8	DABCO	85
9	NaOMe	47
10	K_2CO_3	40
11	$\text{K}_3\text{PO}_4 \cdot 3\text{H}_2\text{O}$	30
12	NaOH	31

Reaction conditions: 4-bromoanisole 0.5 mmol, phenylboronic acid 0.75 mmol, Pd/C 1.5 mol%, base 1.0 mmol, H_2O 1.0 mL, 100 °C, in air, 20 min.

3.2. Substrate scope and limitations

With the optimized conditions in hand, we further explored the scope and limitations of this catalytic system; the results are listed in Table 2. Various aryl bromides bearing electron-withdrawing groups, such as nitro, nitrile, and acetyl moieties, and electron-donating groups, such as hydroxyl, methyl, and methoxy moieties, coupled with arylboronic acid with almost complete conversion within 45 min (Table 2, entries 1–7). Arylboronic acids with electron-withdrawing groups such as fluoro and nitrile coupled with 4-bromoanisole to give good to excellent yields on extension of the reaction time (Table 2, entries 8 and 9). This catalytic system followed the basic rule of the Suzuki reaction, i.e., that electron-withdrawing groups on the aryl bromides and electron-donating groups on the arylboronic acids accelerate the rates of the cross-coupling reactions (Table 2, entries 3 and 9). When the steric effect of the aryl bromide or arylboronic acid increased, the cross-coupling reaction proceeded smoothly within 2 h (Table 2, entries 10–14). Increasing the steric effect of both the aryl bromide and arylboronic acid decreased the reactivity of the cross-coupling, but 98% of isolated yield was obtained in 3 h for the reaction between 2-bromobenzonitrile and *o*-tolylboronic acid (Table 2, entry 15). Overall, this catalytic system tolerated a broad range of aryl bromides and arylboronic acids – not only aryl bromides with hydrophilic groups but also with hydrophobic groups.

Aryl-substituted pyridines are the most common *N*-heteroaryl units present in pharmaceutically active compounds. To extend the scope of this methodology, we further investigated the Suzuki reactions of pyridyl bromides with arylboronic acids. 3-Pyridyl bromides were successfully coupled with phenylboronic acid in excellent yields (Table 2, entries 16 and 17). 2-Pyridyl bromide was less active in coupling with arylboronic acids using this catalytic system, providing 50%–86% isolated yields within 24 h (Table 2, entries 18–20). However, the present method is more efficient than our previously result [27] for the cross-coupling of 2-pyridyl bromide with phenylboronic acid, which did not activate 2-pyridyl bromide at all. It should be noted that this catalytic system was also suitable for sulfur-containing heteroaryl bromide. The reaction between 2-bromothiophene and phenylboronic acid gave 83% yield after 4 h (Table 2, entry 21).

The reusability of Pd/C is a great advantage in process chemistry, both economically and environmentally [29–34]. We examined the recyclability of Pd/C in the cross-coupling reaction, using 4-bromobenzonitrile (0.5 mmol) and 4-methylphenylboronic acid (0.75 mmol) as substrates, in the presence of Pd/C (1.5 mol%) and diisopropylamine (two equiv.) at 100 °C in water (1 mL). As shown in Table 3, the recovered Pd/C gave complete conversion within a slightly prolonged period (60 min) for the second run. The catalyst was reused three times without significant loss of catalytic efficiency. From the fourth to the sixth runs, the catalyst still provided 85%, 81%, and 79% isolated yields, respectively, but the efficiency decreased in the seventh run. To identify the actual active catalyst in the Suzuki reaction, Pd/C was pretreated with

Table 2

Pd/C-catalyzed cross-coupling of aryl bromides with arylboronic acids.

$\text{Ar-Br} + \text{R}-\text{C}_6\text{H}_4\text{B(OH)}_2 \xrightarrow[\text{H}_2\text{O}, 100\text{ }^\circ\text{C}]{\text{Pd/C}, (i\text{-Pr})_2\text{NH}} \text{R}-\text{C}_6\text{H}_4\text{Ar}$				
Entry	Ar-Br	Product	Time ^a (min)	Isolated yield (%)
1			20	96
2			20	97
3			45	98
4			20	97
5			20	96
6			30	85
7			20	93
8			120	99
9			120	86
10			120	90
11			120	99
12			60	99
13			60	80
14			60	98
15			180	98
16			240	95
17			30	98
18			1440	57
19			1020	86
20			1440	53
21			240	83

Reaction conditions: aryl bromide 0.5 mmol, arylboronic acid 0.75 mmol, Pd/C 1.5 mol%, (*i*-Pr)₂NH 1.0 mmol, H₂O 1.0 mL, 100 °C, in air.

^a The time was not optimized.

(*i*-Pr)₂NH in neat water for 20 min under the conditions described in Table 3, and passed through a 0.45 μm membrane filter. The filtrate was then used for the Suzuki reaction of

Table 3

Reusability of Pd/C catalytic system.

Run	Isolated yield (%)
1	98
2	98
3	96
4	85
5	81
6	79
7	59

Reaction conditions: 4-bromobenzonitrile 0.5 mmol, 4-methylphenylboronic acid 0.75 mmol, Pd/C 1.5 mmol%, (*i*-Pr)₂NH 1.0 mmol, H₂O 1.0 mL, 100 °C, in air.

4-bromoanisole with phenylboronic acid. However, the reaction was sluggish, and only a trace amount of cross-coupled product was observed after 20 min. These results suggest that the Pd/C-catalyzed Suzuki reaction proceeds heterogeneously, and the active component is Pd located on the carbon; this is consistent with Sajiki's report [29]. The cause of the decrease in catalytic activity is under investigation.

4. Conclusions

A highly efficient, recyclable, and universal protocol has been developed for a Pd/C-catalyzed, ligand-free, aerobic Suzuki reaction without any additives using water as the sole medium. The catalyst was recycled three times without significant loss of catalytic activity. This aerobic and aqueous protocol is in accordance with the concept of green chemistry, and synthetic applications of this approach are currently under investigation in our laboratory.

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Graphical Abstract

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Pd/C-catalyzed ligand-free and aerobic Suzuki reaction in water

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A highly efficient and recyclable catalytic system for the Pd/C-catalyzed, ligand-free Suzuki reaction was developed; a wide range of aryl bromides were tolerated, and the reaction proceeded without any additives in water.

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纯水中有氧条件下Pd/C催化的无配体Suzuki反应

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摘要: 报道一种在纯水中Pd/C催化的高效Suzuki反应体系, 该体系无需除氧, 且无外加配体和添加剂, 底物普适性广泛, 含有亲水或疏水基团的溴代芳烃都能被高效活化. 此外, 对部分杂环芳烃与芳基硼酸的偶联反应也有较好的催化效果. 该催化剂可高效循环使用三次, 且性能无明显下降.

关键词: Suzuki反应; 钯; 碳; 无配体; 二异丙胺; 联芳化合物

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