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Recyclable and highly active cationic 2,2′-bipyridyl palladium(II) catalyst for Suzuki cross-coupling reaction in water

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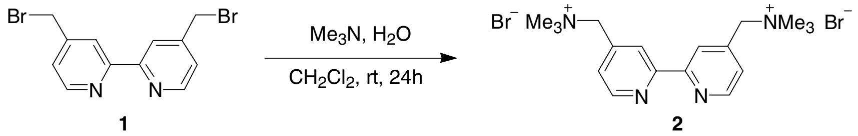
Abstract—A water-soluble and air-stable palladium(II)/cationic 2,2′-bipyridyl catalyst is proven to be a recyclable and extremely active catalyst for Suzuki reaction in aqueous and aerobic conditions. The conveniently prepared catalyst showed little loss in the catalytic process of the coupling between 4-bromoacetophenone and phenylboronic acid after five cycles. For the reactions of aryl chlorides, biaryls were formed in high yields under refluxing temperature in the presence of TBAB.

Suzuki cross-coupling reaction is one of the most important tools for the synthesis of unsymmetrical biaryls,[1] which are widely found in the organic compounds used in agrochemicals, pharmaceutics, natural products, liquid crystalline materials, and conducting polymers.[1e,2] The advantage of the Suzuki cross-coupling reaction is that both reactants of aryl halides and arylboronic acids can tolerate various functional groups. This coupling reaction is usually performed in mixed organic/H_2O solvents. To reduce the consumption of organic solvent, the employment of water-soluble catalysts in aqueous systems has been paid much attention for the advantages of environmental friendly, inflammable, cheap, and recyclable features.[3] Recently, a large variety of auxiliary ligands and palladium catalysts, such as phosphine ligands,[3d,4] di(2-pyridyl)methylamine,[5] palladacycles,[6] Pd/C,[7] catalysts in the mixture of H_2O–surfactants,[8] ligand-free palladium salts,[9] and microwave-promoted reactions,[10] have been developed in order to enable the Suzuki reaction to be performed in neat water to meet the purpose of green chemistry. However, there are only few catalysts with a high efficiency on the coupling of aryl chlorides with arylboronic acids in water under aerobic conditions.[5,6a–d] This is a severe limitation, as from the viewpoint of economics, the use of cheaper aryl chlorides is more suitable for industrial processes. To expand this scope, we prepare a new water-soluble cationic 2,2′-bipyridyl ligand and its palladium complex, which is used to perform as a recyclable and highly active catalyst for the coupling of aryl bromides and chlorides with arylboronic acids into biaryls in water.

The precursor 4,4′-bis(bromomethyl)-2,2′-bipyridine, **1**, was prepared according to the published method.[11] Treatment of **1** (0.5 g, 1.5 mmol) with an excess of Me_3N (50% aqueous solution, 20 mL) in dichloromethane at room temperature for 24 h resulted in the formation of a clear solution. The resulting mixture was freeze-dried to give the cationic 2,2′-bipyridyl ligand, **2**, in a quantitative yield (Scheme 1).[12] Because **2** is soluble in water at room temperature, it is feasible to prepare the catalyst by mixing the equal molar amounts of **2** and dichlorodiammine palladium, $Pd(NH_3)_2Cl_2$, in water directly. The catalyst is stable in air, even in the solution.



Scheme 1.

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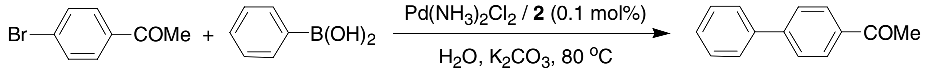
The recyclability of the coupling reaction of phenylboronic acid with 4-bromoacetophenone using K_2CO_3 as a base and 0.1 mol % catalyst was first investigated in water at 80 °C (Scheme 2). The biaryl product was monitored by GC until the complete consumption of aryl bromide. The organic product can be directly separated by filtration, and the aqueous filtrate which contains the catalyst could be re-used for the next run. It was noteworthy that the recycled catalyst provided the cross-coupling product over 90% yields in the five runs, although the extended reaction time to the completion was required. This is mainly due to the work-ups and successive dilution of the catalyst. The employment of various bases such as KOH, K_3PO_4, and KOAc gave similar results. It was found that the use of neutral $PdCl_2(bpy)$ gave only a 49% yield under the comparable reaction conditions, suggesting the ionic nature of the catalyst could be crucial to the reaction.

The variation of aryl bromides was also investigated and the data are collected in Table 1. The reaction of bromobenzene and 4-acetylbenzeneboronic acid with 0.1 mol % catalyst in water under air at 100 °C using K_2CO_3 as the base afforded the product in a 99% yield within 3 h (entry 1). However, only 43% yield was obtained when $Pd(NH_3)_2Cl_2$ was used as the catalyst under the similar conditions (entry 2), indicating that the use with ligand **2** is crucial. As expected, a longer reaction time was required while using 2-substituted aryl bromides (entries 3 and 6) due to the steric reason. In contrast, the reactions of 4-bromoaniline and 4-bromophenol in entries 4 and 7 were faster than that of bromobenzene. This is attributed to their better solubility in aqueous media. A lower loading of catalyst (0.001 mol %) for the reaction of 4-bromophenol with various arylboronic acids has also been studied (entries 8 and 10–12). The reaction for coupling between 4-bromophenol and phenylboronic acid in water with the use of 0.0005 mol % of the catalyst showed TOF up to 81,000 h^{-1}, which was substantially higher than the published data[5b,6e] (entry 9). In addition, the use of 2-bromophenol with a lower loading of the catalyst (0.001 mol %) gave the product in a nearly quantitative yield after the reaction was stirred at 100 °C for 18 h (entry 13). In the cases of bromopyridines, the rate of 3-bromopyridine is much higher than that of 2-bromo-



First cycle: 0.5h, 99%
Second cycle: 1h, 99%
Third cycle: 1.5h, 97%
Fourth cycle: 3h, 94%
Fifth cycle: 6h, 92%

Scheme 2.

Table 1. Suzuki coupling of aryl bromides and arylboronic acids in water[a]

Entry	Ar^1–Br	Ar^2–$B(OH)_2$	[Pd] (mol %)	Time (h)	Yield[c] (%)	TON
1	BrC_6H_5	$4\text{-}MeC(O)C_6H_4B(OH)_2$	0.1	3	99	990
2[b]	BrC_6H_5	$4\text{-}MeC(O)C_6H_4B(OH)_2$	0.1	3	43	430
3	2-Bromomesitylene	$PhB(OH)_2$	0.1	24	86	860
4	$4\text{-}BrC_6H_4NH_2$	$PhB(OH)_2$	0.1	2	86	860
5	$4\text{-}BrC_6H_4OMe$	$PhB(OH)_2$	0.1	12	75	750
6	$2\text{-}BrC_6H_4OMe$	$PhB(OH)_2$	0.1	24	(40)	400
7	$4\text{-}BrC_6H_4OH$	$PhB(OH)_2$	0.1	1	99	990
8	$4\text{-}BrC_6H_4OH$	$PhB(OH)_2$	0.001	1	99	99000
9	$4\text{-}BrC_6H_4OH$	$PhB(OH)_2$	0.0005	2	81	162000
10	$4\text{-}BrC_6H_4OH$	$4\text{-}MeOC_6H_4B(OH)_2$	0.001	24	(95)	95,000
11	$4\text{-}BrC_6H_4OH$	$4\text{-}FC_6H_4B(OH)_2$	0.001	1	64	64,000
12	$4\text{-}BrC_6H_4OH$	$4\text{-}MeC(O)C_6H_4B(OH)_2$	0.001	20	(92)	92,000
13	$2\text{-}BrC_6H_4OH$	$4\text{-}MeC(O)C_6H_4B(OH)_2$	0.001	18	(99)	99,000
14	2-Bromopyridine	$PhB(OH)_2$	0.1	22	(31)	310
15	3-Bromopyridine	$PhB(OH)_2$	0.1	6	(77)	770
16	$4\text{-}BrC_6H_4COMe$	$PhB(OH)_2$	0.01	1	94	9400
17	$4\text{-}BrC_6H_4COMe$	$PhB(OH)_2$	0.001	3	99	99,000
18	$4\text{-}BrC_6H_4COMe$	$4\text{-}MeOC_6H_4B(OH)_2$	0.01	1	84	8400
19	$4\text{-}BrC_6H_4COMe$	$4\text{-}MeOC_6H_4B(OH)_2$	0.001	3	60	60,000
20	$4\text{-}BrC_6H_4COMe$	$4\text{-}FC_6H_4B(OH)_2$	0.01	1	84	8400
21	$4\text{-}BrC_6H_4COMe$	$4\text{-}FC_6H_4B(OH)_2$	0.001	3	99	99,000
22	$4\text{-}BrC_6H_4COMe$	$4\text{-}MeC(O)C_6H_4B(OH)_2$	0.01	1	(97)	9700
23	$4\text{-}BrC_6H_4COMe$	$4\text{-}MeC(O)C_6H_4B(OH)_2$	0.001	3	(99)	99,000
24	$4\text{-}BrC_6H_4COOH$	$PhB(OH)_2$	0.001	1	(97)	97,000
25	$4\text{-}BrC_6H_4COOH$	$PhB(OH)_2$	0.0002	5	(79)	395,000
26	$4\text{-}BrC_6H_4CF_3$	$PhB(OH)_2$	0.1	12	99	990

[a] Reaction conditions: aryl bromide (1 mmol), arylboronic acid (1.3 mmol), K_2CO_3 (2 mmol), H_2O (3 mL), 100 °C in air.

[b] $Pd(NH_3)_2Cl_2$ was used in the absence of ligand **2**.

[c] GC yields using *n*-hexadecane as internal standard based on aryl bromides, isolated yields are given in parentheses.

Table 2. Suzuki coupling of aryl chlorides and arylboronic acids in water[a]

Entry	Ar^1–Cl	Ar^2–$B(OH)_2$	[Pd] (mol %)	T (°C)	Time (h)	Yield[c] (%)
1	$4\text{-}ClC_6H_4NO_2$	$PhB(OH)_2$	0.5	100	3	99
2	$4\text{-}ClC_6H_4NO_2$	$PhB(OH)_2$	0.1	140	12	70
3[b]	$4\text{-}ClC_6H_4NO_2$	$PhB(OH)_2$	0.1	140	12	99
4[b]	$4\text{-}ClC_6H_4NO_2$	$PhB(OH)_2$	0.01	140	24	70
5	$4\text{-}ClC_6H_4NO_2$	$4\text{-}MeOC_6H_4B(OH)_2$	0.5	100	8	(97)
6	$4\text{-}ClC_6H_4NO_2$	$4\text{-}FC_6H_4B(OH)_2$	0.5	100	6	(97)
7	$4\text{-}ClC_6H_4NO_2$	$4\text{-}MeC(O)C_6H_4B(OH)_2$	0.5	100	4	(92)
8	$2\text{-}ClC_6H_4NO_2$	$PhB(OH)_2$	0.5	100	12	(95)
9[b]	$4\text{-}ClC_6H_4COMe$	$PhB(OH)_2$	1	140	6	99
10	$4\text{-}ClC_6H_4COMe$	$PhB(OH)_2$	0.01	140	12	81
11[b]	$4\text{-}ClC_6H_4COMe$	$4\text{-}MeOC_6H_4B(OH)_2$	1	140	12	99
12[b]	$4\text{-}ClC_6H_4COMe$	$4\text{-}FC_6H_4B(OH)_2$	1	140	7	99
13[b]	$4\text{-}ClC_6H_4COMe$	$4\text{-}MeC(O)C_6H_4B(OH)_2$	1	140	5	(99)
14[b]	$2\text{-}ClC_6H_4COMe$	$PhB(OH)_2$	1	140	18	(98)
15[b]	$4\text{-}ClC_6H_4CN$	$PhB(OH)_2$	1	140	24	99
16[b]	$2\text{-}ClC_6H_4CN$	$PhB(OH)_2$	1	140	7	98
17[b]	Chlorobenzene	$4\text{-}MeOC_6H_4B(OH)_2$	1	140	48	50
18[b]	$2\text{-}ClC_6H_4OH$	$4\text{-}MeC(O)C_6H_4B(OH)_2$	1	140	9	(99)

[a] Reaction conditions: aryl chloride (1 mmol), arylboronic acid (1.3 mmol), K_2CO_3 (2 mmol), TBAB (0.5 mmol), H_2O (3 mL).
[b] 1 mmol TBAB is used as additive.
[c] GC yields using *n*-hexadecane as internal standard based on aryl chlorides. Isolated yields are given in parentheses.

pyridine (entry 14 and 15). As for the aryl bromides bearing electron-withdrawing groups, the loading of catalyst can also be reduced to 0.001 mol % and good to high yields were obtained in a short reaction time (entry 17, 19, 21, and 23–24). Since 4-bromobenzoic acid is soluble in basic aqueous media the loading of catalyst was further reduced to 0.0002 mol %, we found that a 79% yield was obtained in 5 h corresponding to a TON: 395,000 (entry 25). The longer reaction time for the coupling of 4-bromobenzotrifluoride with phenylboronic acid was probably due to its poor solubility (entry 26).

Apparently, the solubility of aryl bromides is to affect the reaction rates. 4-Bromophenol and 4-bromobenzoic acid that are soluble in the basic aqueous phase, thus facilitate the oxidative addition (entries 9 and 25).

The reactivity of aryl chlorides was also studied. The reaction of 4-chloronitrobenzene with phenylboronic acid at 100 °C in the presence of 0.5 mol % of catalyst gave no product after 1 day. To circumvent this problem, tetra-*n*-butylammonium bromide (TBAB) was employed as an additive, and the results are shown in Table 2.

In the presence of 50 mol % TBAB the coupling of 4-chloronitrobenzene with phenylboronic acid resulted in the formation of cross-coupling product in a 99% GC yield in 3 h with 0.5 mol % catalyst at 100 °C (entry 1). It was found that the amount of addition of TBAB is crucial in the cross-coupling reaction of aryl chlorides and arylboronic acids. When the reaction temperature was elevated to 140 °C, a better result was obtained with the use of 100 mol % of additive (entries 2–3). In the similar fashion, the loading of catalyst could be reduced to 0.01 mol % giving 4-nitrobiphenyl in a 70% yield (entry 4). Furthermore, 4- and 2-Chloronitrobenzenes could also react with electron-rich and electron-poor arylboronic acids in water at 100 °C to afford the corresponding products in excellent yields (entries 5–8). Different substituted chloroacetophenones were transformed efficiently into the corresponding biaryls with 1 mol % catalyst (entry 9 and 11–14). High TON: 8100 was obtained by using 0.01 mol % catalyst for the reaction of 4-chloroacetophenone with phenylboronic acid (entry 10). Other activated aryl chlorides, such as 4- and 2-chlorobenzonitriles, were coupled efficiently with phenylboronic acid using 1 mol % catalyst (entries 15–16). Finally, we studied the reactivity of unactivated aryl chlorides and we observed that chlorobenzene gave a moderate yield after 48 h (entry 17). 2-Chlorophenols, due to good solubility in water, afforded an excellent yield after 9 h at 140 °C (entry 18).

In summary, a water-soluble Pd(II)/cationic 2,2′-bipyridyl catalyst is developed. This exhibits recyclability and a high efficiency for the coupling of activated and deactivated aryl bromides and chlorides with various arylboronic acids in water under aerobic conditions. This environmental friendly procedure using water as the solvent makes it potentially for industrial applications. The further studies of other organic carbon–carbon bond formations catalyzed by this system are currently under investigation.

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12. The spectral data of cationic 2,2′-bipyridyl ligand **2**: ^{1}H NMR (D_2O): δ 3.16 (s, 18H), 5.07 (s, 4H), 7.65 (d, $J = 5.1$ Hz, 2H), 8.24 (s, 2H), 8.75 (d, $J = 5.1$ Hz, 2H); ^{13}C NMR (acetone-*d*): δ 52.1 (6C), 66.6 (2C), 124.2 (2C), 126.8 (2C), 136.5 (2C), 148.6 (2C), 153.7 (2C); FAB-MS: *m*/*z*: 379, 381 [$M^+ - Br$] (calcd: 379, 381).