Room-temperature highly efficient Suzuki–Miyaura reactions in water in the presence of Stilbazo†

Yi-Yuan Peng,*[a,b] Jinbiao Liu,[a] Xiaoli Lei[a] and Zenlan Yin[a]

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An efficient catalytic system for the ligand-free Suzuki–Miyaura reaction in water at room temperature is disclosed, promoted by Stilbazo (stilbene-4,4′-bis[(1-azo)-3,4-dihydroxybenzene]-2,2′-disulfonic acid diammonium salt). The desired carbon–carbon bond formation proceeded well under mild conditions with high efficiency and good functional group tolerance.

Introduction

Among transition-metal catalyzed cross-coupling reactions, the Suzuki–Miyaura coupling is probably the most widely used in both laboratory and industry, due to the great functional group tolerance of this transformation and the innocuous nature of many boronic acids, which are generally non-toxic‡ and stable to heat, air and moisture.[1] The Suzuki–Miyaura coupling of organic (pseudo)halides with boronic acids is now an important method for the selective construction of biaryls,[1,2] and has found extensive use in the synthesis of natural products, pharmaceuticals, and advanced materials.[3] Usually, the traditional Suzuki–Miyaura coupling procedure involves the use of a palladium–ligand complex (the ligand often being a phosphine) as a catalysts. However, many of these complexes are sensitive to both air and moisture, and thus the reactions are performed under oxygen-free conditions to avoid side-reactions. Moreover, their cost and toxicity limit large-scale industrial applications.[4] Therefore, the development of efficient and ligand-free systems for the Suzuki–Miyaura reaction under mild conditions is of current interest.

The use of water as solvent for the Suzuki reaction has received much attention.[5] Water has clear advantages as a solvent in organic synthesis because of its safety, cost, and application to environmentally benign processes.[6] Recently, non-phosphine Suzuki reaction catalysts involving ligands such as *N*-heterocyclic carbenes[7] (some forming palladacycle species[8]) have been reported to be active in mixed organic–aqueous solvents.[8a,9,10] However, the activity of these systems remains too low to be industrially viable, and reaction in the absence of ligands is greatly limited in aqueous media. Many additives[11] and water-soluble ligands[12] have also been applied successfully in the Suzuki reaction as useful promoters. However, reaction in the absence of additives and ligands is greatly limited by the substrate solubility in aqueous media. The problem of low substrate solubility in water can certainly be overcome to some extent by the use of phase-transfer catalysts[11,13] and mixed organic–aqueous solvent systems.[14]

Stilbazo, (stilbene-4,4′-bis[(1-azo)-3,4-dihydroxybenzene]-2,2′-disulfonic acid diammonium salt) (Fig. 1), an anionic dye, has been studied spectrophotometrically and found to form colored complexes with several metals.[15] We envisioned that Stilbazo may function both as a ligand and as a surfactant for aqueous reaction. By a preliminary experiment, we found that the Suzuki–Miyaura reaction in water using Stilbazo as a promoter worked very well. As part of a continuing effort in our laboratory toward the development of new methods in green process,[16] we herein disclose a novel protocol for the Suzuki–Miyaura reaction in water using Stilbazo as a promoter. The desired carbon–carbon bond formation proceeded under mild conditions with high efficiency and good functional group tolerance.

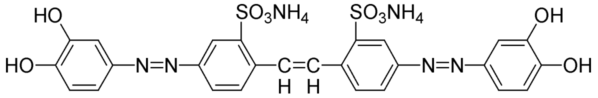

Fig. 1 The structure of Stilbazo.

Results and discussion

Optimization of the coupling reaction conditions

At the outset, 4-iodoanisole **1a** and phenylboronic acid **2a** were employed as the substrates for reaction development. Results of this preliminary survey are shown in Table 1. In an initial experiment, the reaction occurred in the presence of Et_3N and 5 mol% $Pd(OAc)_2$ in DMF at room temperature. After 4 h, the coupling product **3a** was isolated in 55% yield (Table 1, entry 1). The yield improved to 76% when 10 mol% of Stilbazo was used (entry 2). Further screening of solvents revealed that water was the best choice (entry 6). Parameters including bases

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[a] *Key Laboratory of Green Chemistry of Jiangxi Province and College of Chemistry, Jiangxi Normal University, Nanchang, 330022, China. E-mail: yypeng@jxnu.edu.cn, yiyuanpeng@yahoo.com; Fax: +86 791-8120386; Tel: +86 791-8120386*
[b] *College of Life Science, Jiangxi Normal University, Nanchang, 330022, China*

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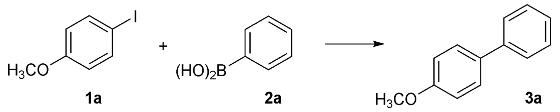
‡ Although boronic acids are in general non-toxic, 50% of aryl boronic acids are mutagenic.

Table 1 Optimization of the reaction conditions[a]



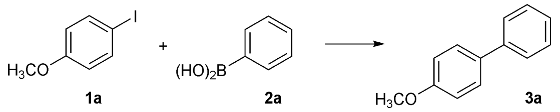
Entry	Catalyst	Base	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$	Et_3N	DMF	55
2	$Pd(OAc)_2$/I	Et_3N	DMF	76
3	$Pd(OAc)_2$/I	Et_3N	THF	61
4	$Pd(OAc)_2$/I	Et_3N	Dioxane	66
5	$Pd(OAc)_2$/I	Et_3N	EtOH	50
6	$Pd(OAc)_2$/I	Et_3N	H_2O	85
7	$Pd(OAc)_2$/I	K_3PO_4	H_2O	60
8	$Pd(OAc)_2$/I	NaOH	H_2O	79
9	$Pd(OAc)_2$/I	KOH	H_2O	82
10	$Pd(OAc)_2$/I	Cs_2CO_3	H_2O	80
11	$Pd(OAc)_2$/I	K_2CO_3	H_2O	92
12	$Pd(PPh_3)_4$/I	K_2CO_3	H_2O	86
13	$PdCl_2(PPh_3)_2$/I	K_2CO_3	H_2O	21
14[c]	$Pd(OAc)_2$	K_2CO_3	H_2O	0

[a] *Reaction conditions*: 4-iodoanisole (0.2 mmol), phenylboronic acid (0.3 mmol), $Pd(OAc)_2$ (5 mol%), Stilbazo (10 mol%), solvent (1.0 mL), K_2CO_3 (0.4 mmol), room temperature. [b] Isolated yields. [c] No Stilbazo added.

(entries 7–11) and other palladium catalysts (entries 12 and 13) were investigated subsequently. The reaction worked efficiently when catalyzed by $Pd(OAc)_2$ in the presence of K_2CO_3 as a base (entry 11). A control experiment demonstrated that no reaction took place in water without the addition of Stilbazo (entry 14).

We also explored the effects of the amount of Stilbazo and the ratios of substrates on the model reaction. The results are listed in Table 2. We found that 5 mol% (0.01 M) of Stilbazo (entries 2 and 6) is sufficient, indicating that Stilbazo may function both as the phase transfer catalyst and also as the ligand, since 2.0 mM is enough for the formation of micelles under the phase transfer reactions.[17] A ratio of 4-iodoanisole to phenylboronic acid of 1 : 1.1 is sufficient to guarantee the complete conversion of 4-iodoanisole (entry 6), and the 50 mol% phenylboronic acid can be recycled and reused after isolation by column chromatography (entries 1 and 2).

Table 2 The effect of the amount of Stilbazo and the ratio of substrates on the reaction[a]



Entry	Ratio substrate : boronic acid	Stilbazo (mol%)	Yield (%)[b]
1	1 : 1.5	10	92
2	1 : 1.5	5	93
3	1 : 1.5	2	68
4	1 : 1.5	1	Trace
5	1 : 1.1	10	90
6	1 : 1.1	5	92
7	1 : 1.0	5	80

[a] *Reaction conditions*: 4-iodoanisole (0.2 mmol), $Pd(OAc)_2$ (5 mol%), Stilbazo, water (1.0 mL), K_2CO_3 (0.4 mmol), room temperature. [b] Isolated yields.

The scope of the aryl halides

We chose the optimized reaction conditions as follows: 5 mol% of Stilbazo, 200 mol% K_2CO_3, and 5 mol% $Pd(OAc)_2$ in water at room temperature. A variety of aryl halides and phenylboronic acid were then explored as substrates, and the results are listed in Table 3. We found that aryl bromides and iodides reacted with phenylboronic acid efficiently, giving the corresponding biaryls in good to excellent yields (entries 1–9). Aryl iodides gave higher yields than the corresponding bromides (entries 1–3 *vs.* 6–8). Aryl chlorides did not give any observable desired product, even on heating the reaction mixture to 100 °C and extending the reaction time to 24 h (entry 10). Aryl halides bearing an electron-withdrawing group, such as NO_2 (entry 5) and acetyl (entry 9) gave lower yields. Aryl halides bearing an NH_2 group and heteroaryl halides did not give any of the expected product, and are unsuitable coupling partners in the Suzuki–Miyaura reaction (data not shown). This is probably due to the binding of such substrates to the metal center, resulting in the formation of inactive substrate–metal complexes.[18]

The scope of arylboronic acids

To further extend the scope of our Pd catalytic system in water, we next investigated the coupling reactions of aryl bromides and iodides with other arylboronic acids, such as *p*-methylphenylboronic acid, *p*-chlorophenylboronic acid, and *p*-(*N*,*N*-dimethylamino)phenylboronic acid. The reactions all proceeded very well and gave the corresponding coupling products in good to excellent yield (Table 3, entries 11–21).

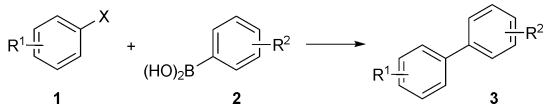
The reactions of 5-indolylboronic acid

Recently, highly active catalysis systems have been reported for the Suzuki reaction of heteroaryl halides and heteroarylboronic acids, and significant improvements have been achieved in the presence of phosphine ligands.[19] However, only a few examples have been reported of the coupling of indolylboronic acids.[19j] In the current system, we were therefore surprised to find that the coupling reactions proceeded very well when 5-indolinylboronic acid was used as the substrate. Reactions using aryl iodides/bromides (whether they bear a strongly electron-withdrawing group, such as NO_2, or an electron-donating group, such as NH_2) and heteroaryl halides proceeded efficiently, and afforded the corresponding 5-arylindolines in good to excellent yields (Table 4, entries 1–14). We envisioned that indole itself may be functioning as a ligand in the reactions, so we investigated the function of indole in the coupling reaction. The reaction of 4-nitroiodobenzene and phenylboronic acid afforded the product **3e** in only 33% yield within 30 h under the optimized conditions (Table 2, entry 5). However, when 20 mol% indole was added to the reaction, the reaction was complete within 3 h, and gave **3e** in 81% yield (Table 4, entry 15).

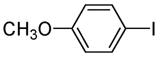
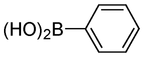
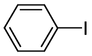
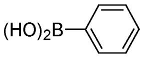
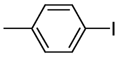
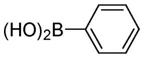
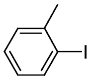
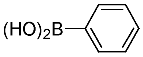
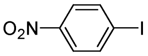
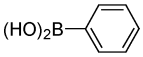
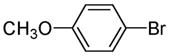
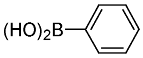
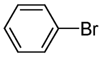
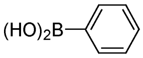
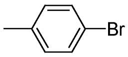
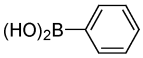
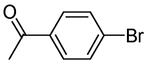
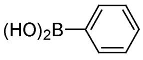
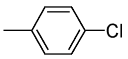
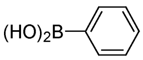
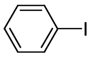
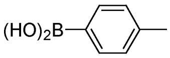
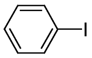
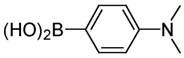
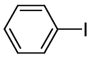
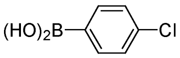
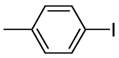
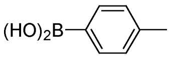
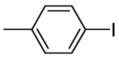
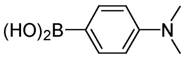
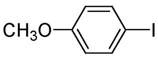
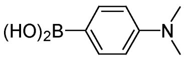
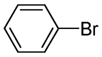
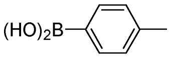
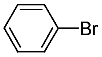
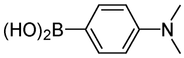
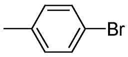
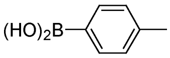
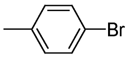
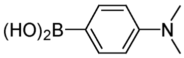
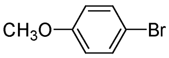
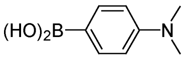
Conclusions

We have disclosed an efficient catalytic system for the ligand-free Suzuki–Miyaura reaction in water at room temperature, using Stilbazo as a promoter. The desired carbon–carbon bond formation proceeds well under mild conditions with high

Table 3 The reactions of aryl halides and arylboronic acids under the optimized reaction conditions[a]

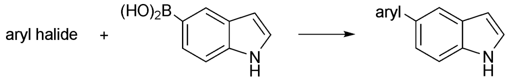


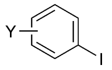
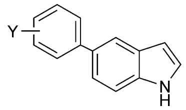
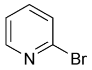
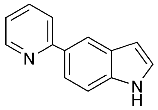
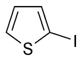
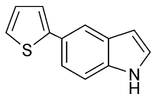
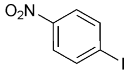
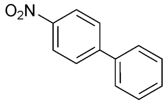
1 2 3

Entry	1	2	Product	Yield (%)[b]
1			**3a**	92
2			**3b**	98
3			**3c**	87
4			**3d**	79
5			**3e**	33
6			**3a**	80
7			**3b**	92
8			**3c**	82
9			**3f**	56
10			**3c**	0
11			**3c**	85
12			**3g**	88
13			**3h**	81
14			**3i**	81
15			**3j**	83
16			**3k**	90
17			**3c**	79
18			**3g**	88
19			**3i**	87
20			**3j**	86
21			**3k**	83

[a] *Reaction conditions*: aryl halide (0.2 mmol), arylboronic acid (0.22 mmol), $Pd(OAc)_2$ (5 mol%), Stilbazo (5 mol%), water (1.0 mL), K_2CO_3 (0.4 mmol), room temperature. [b] Isolated yield based on the aryl halides.

Table 4 The coupling reaction of 5-indolinylboronic acid with a variety of aryl halides[a]



	Aryl halide			
Entry	X	Y	Product	Yield (%)[b]
				
1	I	H	**4a**	92
2	I	*p*-Me	**4b**	89
3	I	*p*-OMe	**4c**	98
4	I	*p*-NO_2	**4d**	81
5	I	*p*-NH_2	**4e**	83
6	I	*p*-NMe_2	**4f**	81
7	I	*o*-Me	**4g**	50
8	Br	H	**4a**	80
9	Br	*p*-Me	**4b**	70
10	Br	*p*-NO_2	**4d**	85
11	Br	*p*-MeCO	**4h**	77
12	Br	*p*-NH_2	**4e**	74
13			 **4i**	68
14			 **4j**	72
15[c]			 **3e**	81

[a] *Reaction conditions*: aryl halide (0.2 mmol), 5-indolinylboronic acid (0.22 mmol), $Pd(OAc)_2$ (5 mol%), Stilbazo (5 mol%), water (1.0 mL), K_2CO_3 (0.4 mmol), room temperature. [b] Isolated yields. [c] 20 mol% indole was added to the reaction system.

efficiency and good functional group tolerance, giving the biaryl compounds in good to excellent yield.

Experimental section

In the optimized procedure, Stilbazo (5 mol%) was added to a mixture of the aryl halide (0.2 mmol) and arylboronic acid (0.22 mmol), K_2CO_3 (0.4 mmol) and H_2O (1 mL) in a 5 mL round-bottomed flask filled with N_2. The reaction mixture was stirred at room temperature until complete conversion of aryl halide had taken place (monitored by TLC). After completion, the mixture was extracted with CH_2Cl_2 (3 × 3 mL) and the combined organic extracts were dried over anhydrous sodium sulfate and evaporated under vacuum, leaving the crude product, which was purified by column chromatography. All products have been reported previously,[18] and their identities were confirmed by ^1H NMR and ^{13}C NMR spectroscopy.

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