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A General catalyst for Suzuki–Miyaura and Sonogashira reactions of aryl and heteroaryl chlorides in water

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Abstract

We report the synthesis of 2-(3-sulfonatomesityl)-5-sulfonatoindenyl)dicyclohexylphosphine hydrate sodium salt and its use in palladium-catalyzed Suzuki–Miyaura and Sonogashira coupling reactions in water (and biphasic water–organic solvent mixtures) to prepare a variety of functionalized biaryls and aryl alkynes in excellent yield.

Introduction

During the last two decades, there has been an increasing interest in the use of water as a solvent for many reactions using homogeneous catalysis.¹ Cost, environmental benefits and safety are some of the reasons used to justify the replacement of organic solvents by water in many synthetic transformations. The use of water in Pd-catalyzed cross-coupling reactions dates back to the early development of the Suzuki–Miyaura

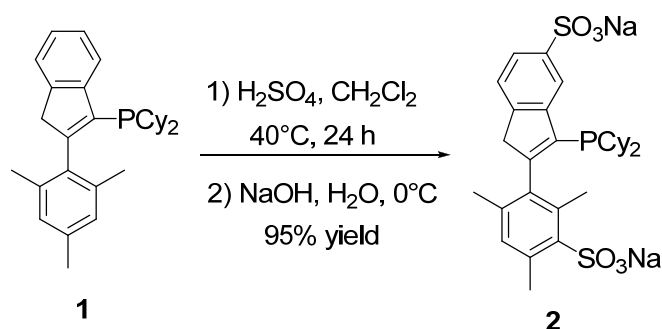
reaction,² with the first example reported by Calabrese and co-workers in 1990.³ Since then, a large number of methods for coupling reactions using water as the reaction solvent have been developed, including microwave-heating,⁴ ultrasonic-irradiation,⁵ ligand-free methodology,⁶ water-soluble catalysts,⁷ nano catalysts,⁸ and the addition of organic co-solvents,⁹ surfactants¹⁰ or phase-transfer reagents.¹¹ Several reviews have been devoted to this subject.¹²

However, only a few examples have been reported concerning palladium-catalyzed coupling reactions of hydrophilic aryl and heteroaryl chlorides with aryl boronic acids in purely aqueous reaction media.¹³ Several sulfonated phosphine derivatives have been prepared and used in coupling reactions conducted in water and biphasic water–organic solvent systems.¹⁴ Shaughnessy and co-workers reported the use of sterically demanding, water-soluble, alkylphosphine salts in the Suzuki–Miyaura, Sonogashira, and Heck reactions of unactivated aryl bromides to provide the products derived of the carbon–carbon bond forming reactions in excellent yield. However, the limitations to this methodology include a lengthy synthesis and the poor thermal and air stability of the ligand. In addition, only a single example of a substituted aryl chloride was described.¹⁵ The biaryl sulfonated phosphine–Pd catalysts displayed high activity in the Suzuki–Miyaura reaction of aryl chlorides in water and in the Sonogashira reaction using a mixture of water and acetonitrile as solvent. However, this reaction system, as reported, was not general for heteroaryl chlorides.¹⁶ As part of our ongoing interest in palladium-catalyzed reactions,¹⁷ we now report the Suzuki–Miyaura and Sonogashira reaction of aryl and heteroaryl chlorides catalyzed by an air-stable sulfonated indenyl phosphine/Pd-catalyst system using water as the reaction solvent.

Results and Discussion

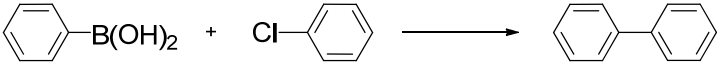
The structure of compound (2-mesitylindenyl)dicyclohexylphosphine (**1**) is similar to Buchwald's biaryl dialkyl monophosphine ligands.¹⁶ We envisaged that the electron-rich lower aromatic ring in **1** could be functionalized with a

water-solubilizing sulfonate group. In fact, treatment of compound **1** with concentrated H_2SO_4 at $40\text{ }^\circ\text{C}$ for 24 h gave compound **2** derived from the unexpected disulfonation reaction occurring at the C5-position on the indenyl ring and the C3'-position on phenyl ring in 95% yield after treatment with NaOH and work-up (Scheme 1).



Scheme 1. Synthesis of compound **2**

To test the effectiveness of this new ligand **2**, the coupling reaction between phenylboronic acid and chlorobenzene was investigated (Table 1). The reactions were performed in water at $100\text{ }^\circ\text{C}$ for 8 h in the presence of 0.50 mol% $\text{Pd}(\text{OAc})_2$ as catalyst. First the reaction was conducted without any base and/or phosphine ligand **2** and no product was obtained (Table 1, entries 1–3). Then 1.0 mol% phosphine ligand **2** and 3.0 equivalent $\text{K}_3\text{PO}_4 \cdot 3\text{H}_2\text{O}$ were used and 13% yield of the coupling product was observed (Table 1, entry 4). Base was found to be crucial for a high yield. While strong bases such as NaOH and KOH provided almost no desired product (Table 1, entries 5 and 6), weak bases such as KOAc, Cs_2CO_3 , Na_2CO_3 and K_2CO_3 gave low to moderate yields (Table 1, entries 7–10). Among various bases employed, K_2CO_3 proved to be most efficient and provided 38% yield. The Pd/ligand ratio of 1:3 showed the best yield whereas ratios of 1:2 and 1:4 provided lower substrate conversions (Table 1, entries 10–12). The effectiveness of the reaction time was then investigated. 24 h was found to be the reaction time of choice for this catalytic system (Table 1, entries 11, 13 and 14).

Table 1. Initial screening of Suzuki-Miyaura cross-coupling reaction of phenylboronic acid with chlorobenzene^a


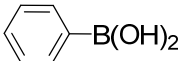
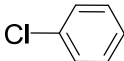
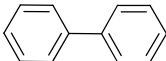
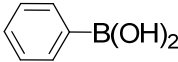
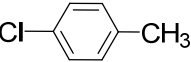
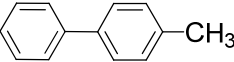
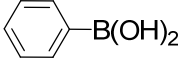
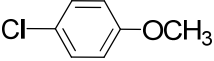
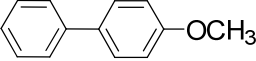
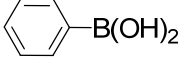
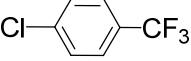
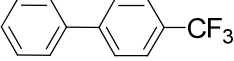
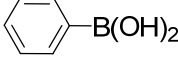

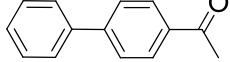
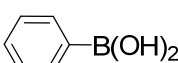
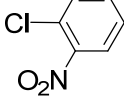
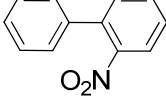
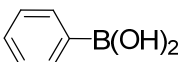
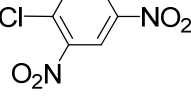
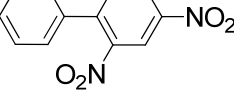
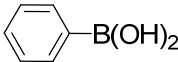
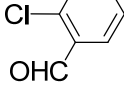
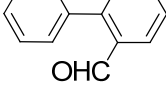
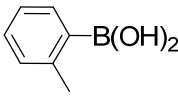
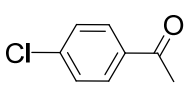
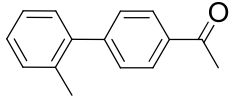
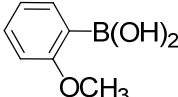
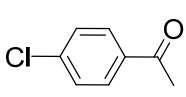
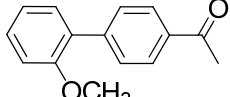
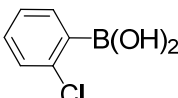
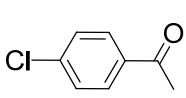
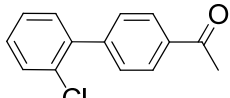
Entry	Pd(OAc) ₂ (mol%)	Ligand 2 (mol%)	Base	Time (h)	Yield ^b (%)
1	0.50	–	–	8	0
2	0.50	–	K ₃ PO ₄ ·3H ₂ O	8	0
3	0.50	1.00	–	8	0
4	0.50	1.00	K ₃ PO ₄ ·3H ₂ O	8	13
5	0.50	1.00	NaOH	8	<5
6	0.50	1.00	KOH	8	<5
7	0.50	1.00	KOAc	8	13
8	0.50	1.00	Cs ₂ CO ₃	8	10
9	0.50	1.00	Na ₂ CO ₃	8	26
10	0.50	1.00	K ₂ CO ₃	8	38
11	0.50	1.50	K ₂ CO ₃	8	64
12	0.50	2.00	K ₂ CO ₃	8	50
13	0.50	1.50	K ₂ CO ₃	16	70
14	0.50	1.50	K ₂ CO ₃	24	78

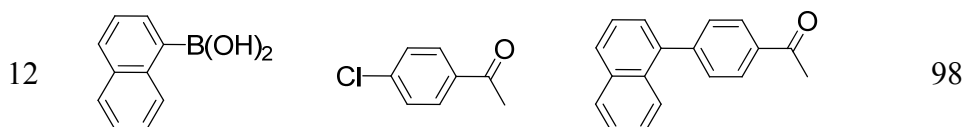
^aReaction conditions: Phenylboronic acid (1.2 mmol), chlorobenzene (1.0 mmol), Pd(OAc)₂ (0.5 mol%), ligand **2**, base (3.0 mmol), H₂O (1.5 mL), 100 °C. ^bIsolated yield.

Using the optimized reaction conditions based on ligand **2**, we investigated the coupling of both hydrophobic and hydrophilic substrates (Table 2). The coupling of phenylboronic acid and electronically neutral chlorobenzene at 100 °C using water as the solvent provided the corresponding biaryl product in 78% yield (Table 2, entry 1). The reaction of phenylboronic acid with aryl chlorides bearing electron-donating substituents such as –CH₃ and –OCH₃ at the *para* position gave the desired products in moderate yield (Table 2, entries 2 and 3). The reaction of aryl chlorides bearing electron-withdrawing groups such as –CF₃, –COCH₃, –NO₂, –CHO were also tolerated in the cross-coupling reaction with phenylboronic acid and gave the desired products in moderate to high yield under the optimized reaction conditions (Table 2, entries 4–8). This catalyst system can also be used in the coupling reactions of

moderately hindered aryl boronic acids with aryl chlorides. For example, the reaction of 2-methylphenylboronic acid with 4'-chloroacetophenone proceeded smoothly to give the biaryl product in 80% yield (Table 2, entry 9). 2-Methoxyphenylboronic acid, 2-chlorophenylboronic acid and 2-naphthylboronic acid also reacted efficiently with 4'-chloroacetophenone to give the desired products in moderate to good yield (Table 2, entries 10–12).

Table 2. Suzuki–Miyaura cross-coupling reactions of arylboronic acids with aryl halides^a

		0.5 mol% Pd(OAc) ₂ , 1.5 mol% 2			
		ArB(OH) ₂ + Ar'X		→ Ar–Ar'	
		3 equiv. K ₂ CO ₃ , 1.5 mL H ₂ O			
Entry	ArB(OH) ₂	Ar'X	Product	Yield (%) ^b	
1				78	
2				43	
3				76	
4				82	
5				97	
6				97	
7				81	
8				95	
9				80	
10				60	
11				83	

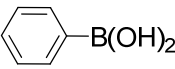
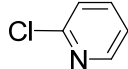
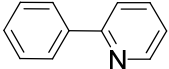
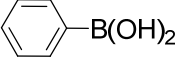
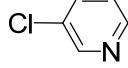
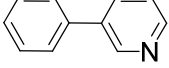
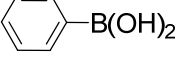
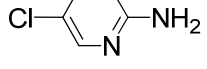
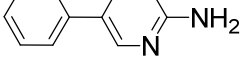
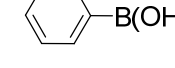
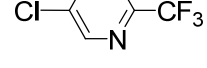
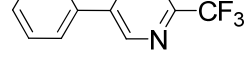
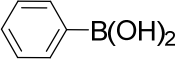
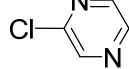
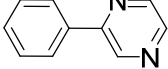


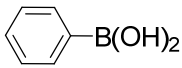
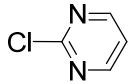
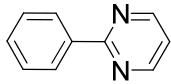
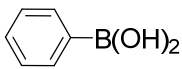
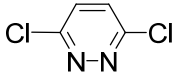
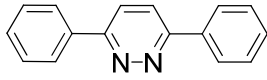
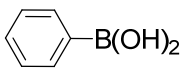
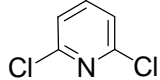
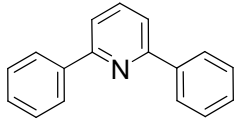
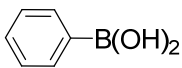
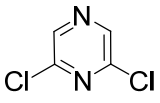
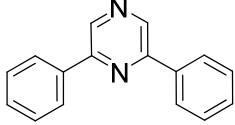
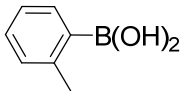
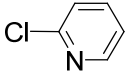
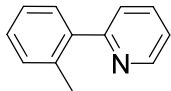
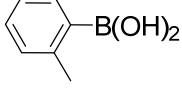
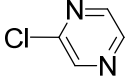
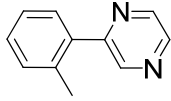
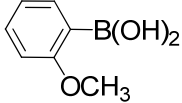
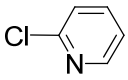
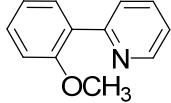
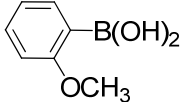
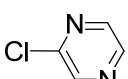
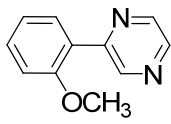
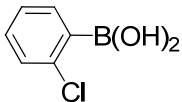
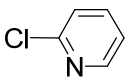
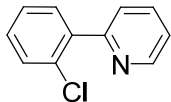
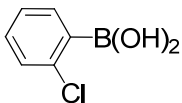
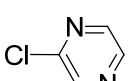
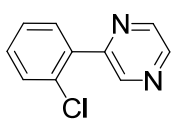
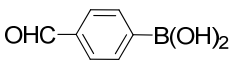
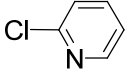
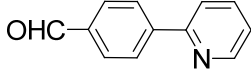
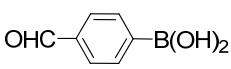
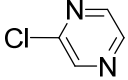
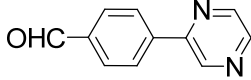
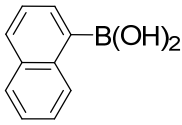
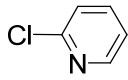
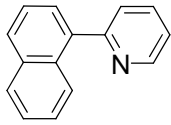
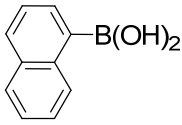
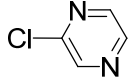
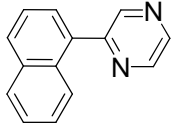
^aReaction conditions: Arylboronic acid (1.2 mmol), aryl chloride (1.0 mmol), Pd(OAc)₂ (0.5 mol%), **2** (1.5 mol%), K₂CO₃ (3.0 mmol), H₂O (1.5 mL), 100 °C, 24 h. ^bIsolated yield.

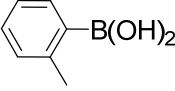
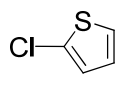
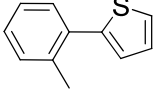
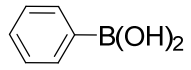
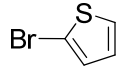
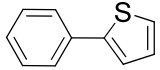
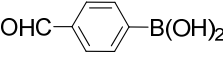
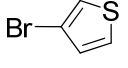
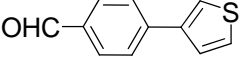
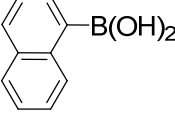
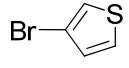
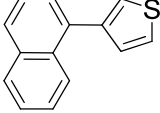
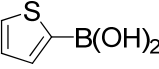
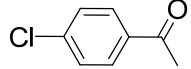
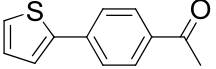
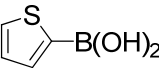
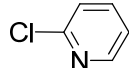
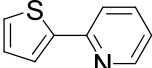
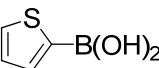
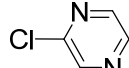
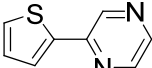
Heterocyclic compounds are of particular interest to the pharmaceutical industry.¹⁸ The application of heterocyclic compounds in cross-coupling reactions still remains a synthetic challenge,¹⁹ because the ligating ability of the heteroatoms present can lead to catalyst deactivation. In addition the electronic properties at certain positions in heterocycles can be unfavorable for the elementary reactions required for these catalytic processes.²⁰ To the best of our knowledge, only a few examples of aqueous-phase Suzuki–Miyaura reactions of heteroaryl chlorides have been published.^{16,21} We have examined the use of compound **2** as the ligand in the Suzuki–Miyaura reaction of a range of challenging hydrophilic heteroaryl halides (Table 3). As shown in Table 3, our catalytic system works well for a number of different heteroaryl chlorides and bromides, including pyridine, pyrazine, pyrimidine, pyridazine and thiophene derivatives. For example, phenylboronic acid underwent the desired cross-coupling reaction with 2-chloropyridine and 3-chloropyridine to afford the corresponding products in good to excellent yield (Table 3, entries 1, 2). Typically, the coupling of heteroaryl chlorides bearing an unprotected amino group is slowed down due to competitive binding of the amino group to the Pd center of the catalyst. Catalyst deactivation has been noted with this kind of substrate.²² Interestingly, our catalytic system was successful in the coupling reaction of unprotected 2-amino-5-chloropyridine (Table 3, entry 3). Other heteroaryl chlorides such as 3-chloro-6-(trifluoromethyl) pyridine, 2-chloropyrazine and 2-chloropyrimidine were converted into the desired products in moderate to excellent yield (Table 3, entries 4–6). In addition, our catalyst system could be applied to the double coupling reaction of phenylboronic acid with 3,6-dichloropyridazine, 2,6-dichloropyridine and

2,6-dichloropyrazine, providing the triaryl products in moderate to high yield (Table 3, entries 7–9). To determine the scope of this process, we examined the reaction of 2-methylphenylboronic acid, 2-methoxyphenylboronic acid, 2-chlorophenylboronic acid, 4-formylphenylboronic acid and 2-naphthylboronic acid with nitrogen-containing heteroaryl chlorides. All these coupling reaction proceeded smoothly in moderate to high yield (Table 3, entries 10–19). To further extend the scope reactions using our catalytic system, we investigated the cross-coupling reaction of unactivated thiophene halides. Unfortunately, 2-methylphenylboronic acid coupled with 2-chlorothiophene to give the thiophene derivative in a low 22% yield (Table 3, entry 20). However, the cross-coupling reaction of arylboronic acid with 2- and 3-bromothiophenes proceeded very well in moderate to good yield (Table 3, entries 21–23). In addition, we investigated the coupling reaction of 2-thiophenylboronic acid with aryl chlorides with moderate yields (41–50%) being obtained in the case of 4'-chloroacetophenone and 2-chloropyridine (Table 3, entries 24, 25). However, in the case of 2-chloropyrazine, the coupling reaction gave the desired product in an excellent 87% yield (Table 3, entry 26).

Table 3. Suzuki–Miyaura cross-coupling reactions of arylboronic acids with heteroaryl halides^a

		0.5 mol% Pd(OAc) ₂ , 1.5 mol% 2			
		ArB(OH) ₂ + Ar'X		Ar–Ar'	
		3 equiv. K ₂ CO ₃ , 1.5 mL H ₂ O			
Entry	ArB(OH) ₂	RX	Product	Yield (%) ^b	
1				96	
2				80	
3				75	
4				90	
5				95	

6				70
7				42 ^c
8				96 ^c
9				93 ^c
10				66
11				90
12				53
13				91
14				35
15				96
16				93
17				90
18				95
19				96

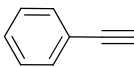
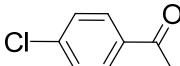
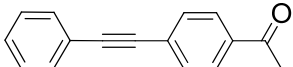
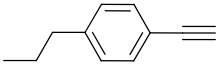
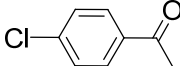
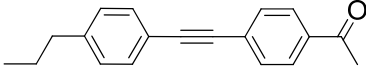
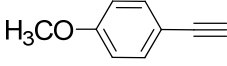
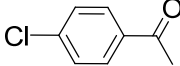
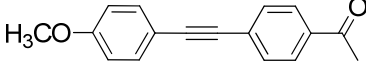
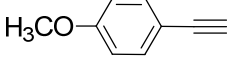
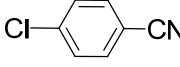
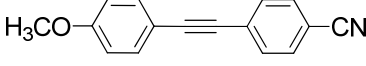
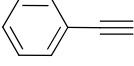
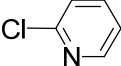
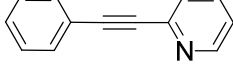
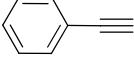
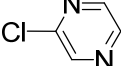
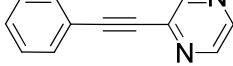
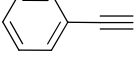
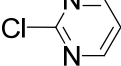
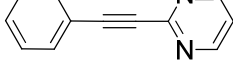
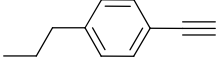
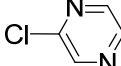
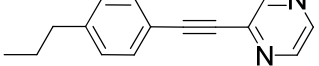
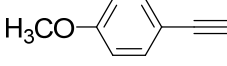
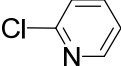
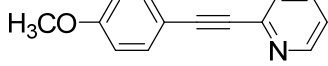
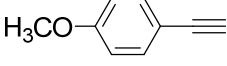
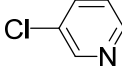
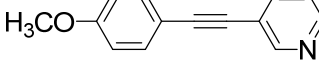
20				22
21				93
22				79
23				54
24				50
25				41
26				87

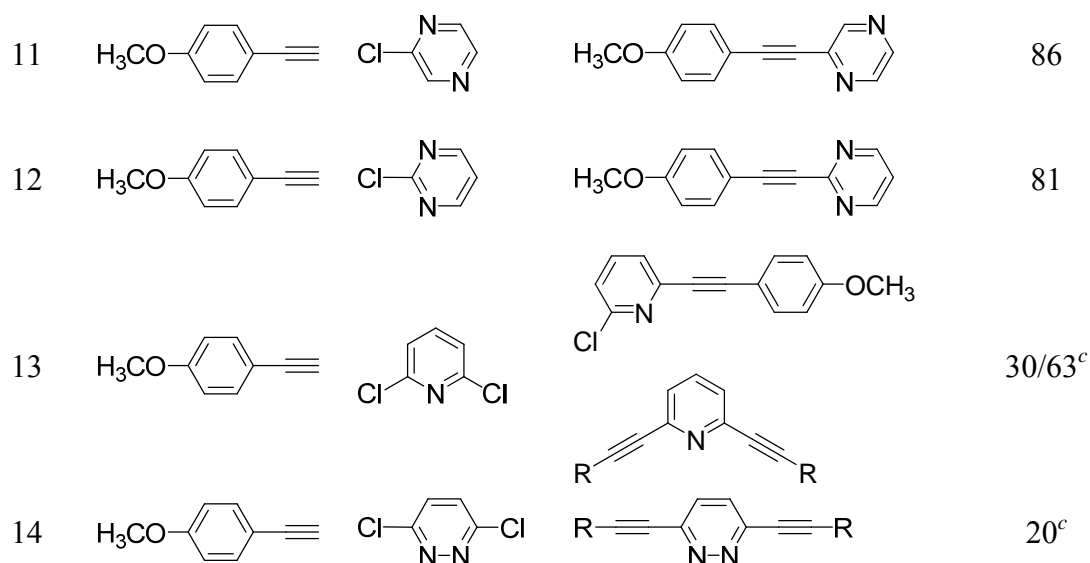
^aReaction conditions: Arylboronic acid (1.2 mmol), heteroaryl halide (1.0 mmol), Pd(OAc)₂ (0.5 mol%), **2** (1.5 mol%), K₂CO₃ (3.0 mmol), H₂O (1.5 mL), 100 °C, 24 h. ^bIsolated yield. ^cPhenylboronic acid (2.4 mmol).

The Sonogashira reaction has been one of the most simple and efficient tools for C(sp)²–C(sp²) bond formation and has been widely used towards the synthesis of diaryl acetylenes.²³ Significant progress has been achieved in the coupling reactions of aryl chlorides.²⁴ However, only a few catalyst systems are known to be capable of combining the advantage of using water as the reaction solvent for the Sonogashira reaction of aryl and heteroaryl chlorides.^{16,25} By using a catalyst system based on [PdCl₂(CH₃CN)₂]/**2** and a biphasic water–acetonitrile solvent system,¹⁶ phenyl acetylene was successfully coupled with 4'-chloroacetophenone in 86% yield (Table 4, entry 1). Good yields were obtained for the coupling reactions of hydrophobic 1-ethynyl-4-propylbenzene and 4-ethynylanisole with 4'-chloroacetophenone (Table 4, entries 2 and 3). Moreover, the base-sensitive –CN group was tolerated using our catalytic system (Table 4, entry 4). In addition, phenyl acetylene underwent the desired coupling reactions with 2-chloropyridine, 2-chloropyrazine and 2-chloropyrimidine, affording the corresponding products in moderate to good yield (Table 4, entries 5–7). 1-Ethynyl-4-propylbenzene and 4-ethynylanisole could also

participate in the coupling reaction with heteroaryl chlorides, which proceeded smoothly to afford the corresponding internal alkynes in high yield (Table 4, entries 8–12). Another noteworthy result was the efficient coupling reaction between 4-ethynylanisole with 2, 6-dichloropyridine, both the mono-coupling and double-coupling products were obtained in 30% and 63% yield, respectively (Table 4, entry 13). However, when 4-ethynylanisole was coupled with 3, 6-dichloropyridazine the double coupled product was obtained in low yield (Table 4, entry 14).

Table 4. Sonogashira cross-coupling reactions of aryl halides and heteroaryl halides^a

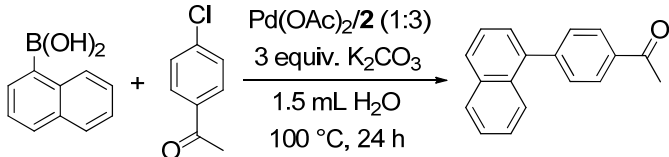
$\text{Ar}-\text{C}\equiv\text{C}-\text{H} + \text{X}-\text{Ar}' \xrightarrow[\text{3 equiv. Cs}_2\text{CO}_3]{\begin{array}{c} 1.0 \text{ mol\% PdCl}_2(\text{CH}_3\text{CN})_2 \\ 3.0 \text{ mol\% } \mathbf{2} \end{array}} \text{Ar}-\text{C}\equiv\text{C}-\text{Ar}'$ 1.5 mL H ₂ O, 1.5 mL CH ₃ CN				
Entry	ArB(OH) ₂	RX	Product	Yield (%) ^b
1				86
2				87
3				85
4				91
5				84
6				89
7				48
8				90
9				94
10				79



^aReaction conditions: Aryl chloride (1.0 mmol), alkyne (1.2 mmol), PdCl₂(CH₃CN)₂ (1.0 mol%), **2** (3.0 mol%), Cs₂CO₃ (3.0 mmol), H₂O (1.5 mL), MeCN (1.5 mL), 100 °C, 24 h. ^bIsolated yield. ^c4-ethynylanisole (2.4 mmol).

To carry out an economical large-scale synthesis of fine chemicals, a low loading catalyst is needed. To further study the efficiency of our catalytic system, we then studied the TON (turnover number) of our catalytic system at low loading. For example, carrying out the Suzuki–Miyaura coupling reaction of 2-naphthylboronic acid with 4'-chloroacetophenone at a palladium loading of 0.05 mol% led to a yield of 86% after 24 h (Table 5, entry 1). This corresponds to a TON of 1 720 mol (ArCl) mol (Pd)⁻¹. When the palladium loading was lowered to 0.005 mol%, the coupling product was still obtained in 52% yield after 24 h (TON = 10 400) (Table 5, entry 2). In addition, the Sonogashira coupling reaction of 4-ethynylanisole with 4'-chloroacetophenone occurred with 0.1 mol% Pd(CH₃CN)₂Cl₂ at 100 °C for 24 h to afford 34% of the product (Table 6, entry 1). This result corresponds to a TON of 340.

Table 5. Suzuki-Miyaura coupling reactions using ultra-low loading of catalyst

			
Entry	Mol% Pd	Yield (%) ^a	TON
1	0.05	86	1 720

2	0.005	52	10 400
3	0.0005	<5	–

^aIsolated yield.

Conclusion

We have demonstrated the use of the sulfonated ligand **2** as a highly active catalytic system for both the Suzuki–Miyaura and Sonogashira coupling reactions, with an unprecedented reactivity and stability for aqueous-phase processes. A variety of aryl and heteroaryl chlorides including activated, deactivated and sterically hindered substrates were coupled successfully using mild reaction conditions. Our approach offers an important and environmentally beneficial alternative in our efforts towards removing the use of organic solvents from organic reactions.

Table 6. Sonogashira coupling reactions using ultra-low loading of catalyst

Entry	Mol% Pd	Yield (%) ^a	TON
1	0.1	34	340
2	0.01	<5	–

^aIsolated yield.

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