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Efficient water-soluble surfactant-type palladium catalyst for Suzuki cross-coupling reactions in pure water at room temperature

Received 00th January 20xx, Accepted 00th January 20xx Pei Qiu,^a Jing Yang Zhao,^a Xu Shi^a and Xin Hong Duan^{b,*}

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Palladium catalyst based on bidentate phosphine-type zwitterionic surfactant as ligand exhibited an excellent catalytic activity in the Suzuki-Miyaura cross couplings. This novel method allowed the reaction of aryl halides with arylboronic acids to occur in pure water at room temperature, forming a variety of biaryls in good to high yields. Heterobiaryls were also efficiently assembled even in the presence of water-insoluble heteroaryl halides as substrates. In addition, such coupling protocol was successfully used to the iterative diarylation of 2,5-dibromopyridine in onepot.

Palladium-catalyzed Suzuki-Miyaura (SM) cross coupling is one of the most powerful transformations for biaryl synthesis in laboratories and industry, as well as in the synthesis of fine chemicals and pharmaceuticals.¹ Typically, such reaction of aryl halides with arylboronic acids occurs in organic solvents such as MeCN, EtOH, DMF and toluene, etc. However, with the increasing demand for green chemistry, water as a nontoxic, inexpensive and safe solvent for organic synthesis has been of widespread interest in recent years.² As such, strategies have been investigated in order to carry out the SM cross coupling reactions in aqueous media.³ Besides heterogeneous catalysis⁴ and the use of surfactants as additives,⁵ a number of watersoluble ligands developed from sulfonating or quaternizing the commonly-used monodentate phosphine ligands in the C-C coupling reactions have been applied to the Pd-catalyzed SM reactions in water.⁶ They include, for example, TPPMS,^{6a} sulfonated biphenyl,^{6b} fluorene^{6c} or dibenzofuran,^{6d} and *t*-Bu-Amphos or *t*-Bu-Pip-Phos^{6e,f} (Scheme 1). Although high activities were obtained in water, these Pd catalytic systems typically required organic co-solvents and/or heating temperatures. Moreover, many such ligands encountered a variety of synthetic challenges and expensive prices. Thus, the





Scheme 1 Representative water-soluble monodentate ligands for the Pd-catalyzed SM cross-couplings in aqueous media.

Zwitterionic surfactants (i.e., bearing both positive and negative charge) display much lower critical micellization concentrations and surface tensions as compared to the conventional ionic surfactants (SDS or CTAB).⁷ In addition, Pd(II) complexes with bidentate phosphine ligands have been shown to be efficient catalysts for C-N coupling reactions.⁸ Motivated by the attractive features of zwitterionic surfactants and bidentate phosphine ligands, we have recently started exploring a simple and novel ligand by integrating a bidentate phosphine ligand into a zwitterionic surfactant, and herein we first report a new in situ-generated catalyst that consists of PdCl₂ and such ligand for the SM cross coupling in pure water at room temperature. The Pd complex carries two substantial benefits. On the one hand, zwitterionic surfactant as ligand leads to relatively high water-solubility of the complex, hence increasing largely the efficiency of the Pd catalysis in pure water. On the other hand, bidentate phosphine-type ligand binds with Pd to form a six-membered ring structure of the active catalytic site,⁹ thereby contributing to the high activity

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⁺ Electronic Supplementary Information (ESI) available: Experimental details and

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and stability of the catalyst. As such, the Pd complex not only is highly efficient catalyst to cross-couple aryl substrates, but also allows the SM reaction of various water-insoluble heteroaryl halides and of 2,5-dibromopyridine by the regioselective diarylation in one pot, which have been no previous report in pure water at room temperature.



The ligand of bidentate phosphine-type zwitterionic surfactant (L) was readily prepared by a two-step procedure. As shown in Scheme 2, [Ph₂P(CH₂OH)₂]Cl was treated successively with sodium 2-aminoethanesulfonate and sodium 2-bromoethanesulfonate to give L in a 75 % total yield.

Table 1 Optimization of the reaction conditions.^a

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	$B(OH)_2$ + $Pd cat.,$ solvent	$\frac{base}{1, r.t.}$ H ₃ C	∞-∕	
Entry	Pd catalyst ^b	Time	Base	Yield ^c
	(mol %)	(h)		(%)
1	PdCl ₂ (2)	12	K_3PO_4	9 (24) ^d
2	PdCl ₂ (2) + SDS (8)	8	K_3PO_4	52
3	PdCl ₂ (2) + CTAB (8)	8	K_3PO_4	60
4	PdCl ₂ (2) + L (8)	6	K ₃ PO ₄	96
5 ^e	PdCl ₂ (2) + L (8)	12	K_3PO_4	54
6	PdCl ₂ (2) + L (8)	6	K ₂ CO ₃	95
7	PdCl ₂ (2) + L (8)	6	NaOH	97
8	PdCl ₂ (2) + L (8)	6	Na ₂ CO ₃	96
9	PdCl ₂ (0.5) + L (2.0)	8	Na ₂ CO ₃	95
10	PdCl ₂ (0.15) + L (0.6)	8	Na ₂ CO ₃	93
11	PdCl ₂ (0.15) + L (0.3)	12	Na_2CO_3	59

^a Conditions: 4-bromophenylethanone (1 mmol), phenylboronic acid (1.5 mmol), base (2 mmol). ^b The PdCl₂/L catalyst was *in-situ* prepared as follows: 1) the mixture of PdCl₂ and L was heated in 3 mL water at 80 °C for 5 min, and until a light brown solution was formed; 2) the resulting solution was cooled down to room temperature. ^c Yield of the isolated product. ^d Yield in refluxing water. MeCN/H₂O (1:1, 3 mL) as solvent.

To probe the catalytic activity of the in situ-generated Pd/L complex and optimal conditions in the SM cross couplings, 4bromoacetophenone and phenylboronic acid were selected as the model substrates¹⁰ (Table 1). At room temperature, in the absence of ligand the reaction with PdCl₂ as catalyst proceeded rather sluggishly in pure water (Table 1, entry 1). Upon using SDS (sodium dodecyl sulfate) or CTAB (hexadecyl trimethyl ammonium bromide) as an additive, only a moderate yield was obtained (Table 1, entry 2 or 3). Interestingly, when L was used as ligand, a complete conversion was achieved within 6 h (Table 1, entry 4). If the same reaction was carried out in MeCN/H₂O, however, the yield of 1a decreased significantly (54 %, Table 1, entry 5). These indicate that L

forms micelles in addition to supporting the Pd catalyst. Therefore, such catalytic system in combination with pure water as solvent is optimal for the reaction at room temperature. Also, bases were screened and found that the bases such as K₃PO₄, K₂CO₃, Na₂CO₃ and NaOH had almost no influence on the catalytic activity (Table 1, entries 4, 6-8). In addition, a much lower catalyst loading of 0.15 mol % turned out to be sufficient for the reaction leading to a high yield of 93 % (Table 1, entry 10 versus entries 8 and 9). At this loading, a 1:4 ratio of Pd:L gave a more active catalysis, while the catalytic activity was significantly diminished at a lower 1:2 ratio (Table 1, entry 11).



² Conditions: the halide (1 mmol), the boronic acid (1.5 mmol), PdCl₂ (0.15 mol-%)/L = 1:4, Na₂CO₃ (2 mmol). ^b Yield of the isolated product. ^c Reaction was performed on 10-mmol scale: 2-bromoaniline (10 mmol), 4-chlorophenylboronic acid (13 mmol), PdCl₂ (0.15 mol-%)/L = 1:4, Na₂CO₃ (18 mmol), H₂O (30 mL), 8 h.

With the above optimized conditions in hand, we next investigated the substrate scope of this catalytic system by Published on 07 June 2016. Downloaded by University of Pittsburgh on 11/06/2016 11:42:27

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using various aryl halides and arylboronic acids as coupling partners, and the results were shown in Table 2. As expected, phenols and benzoic acids were found to be high yielding (Table 2, entries 4 and 5). More importantly, the substrates without hydrophilic substituents could also be well coupled. For example, aldehydes, ketones and esters all proceeded smoothly without competitive side reactions (Table 2, entries 2, 3, 7 and 8). With respect to the substrate 4chlorobenzaldehyde, the catalyst was less effective and only a 21 % yield was reached after 14 h (Table 2, entry 2). Notably, the transformation was insensitive to steric hindrance: as ortho substitution on either the aryl halide or the arylboronic acid was well tolerated (Table 2, entries 4, 5, 7, 8 and 10). In particular, the sterically more hindered 2,4,6-trimethylphenyl bromide also proved to be an efficient substrate (Table 2, entry 6). Moreover, the reaction outcomes were almost not affected by the electronic factors and, for example, the yield of 1h reached 91 % even in the presence of the electron-rich aryl bromide and electron-deficient arylboronic acid as coupling partners (Table 2, entry 7 versus 8). Since the free -NH₂ group was demonstrated to be compatible with this catalytic system (Table 2, entry 9), 4'-chlorobiphenyl-2-amine (1j), an intermediate in the synthesis of the fungicide Boscalid,¹¹ was formed by the direct cross coupling of 2-bromoaniline with 4chlorophenylboronic acid without the need for a nitroreduction step¹² (Table 2, entry 10). To further verify the potential of this catalytic system, the intermediate was prepared on a 10-mmol scale and indeed, the reaction worked as well as on a 1-mmol scale. So, this methodology represents an attractive cross-coupling method for larger-scale application.

Excitingly, the above method was also successfully applied in the synthesis of heterobiaryls, an architectural motif that is ubiquitous in biologically active molecules. However, to date only very few examples of the SM cross couplings of watersoluble heteroaryl halides in water have been published at room temperature.^{3f,6b,13} Obviously when the water-insoluble heteroaryl halides are employed as substrates, the reactions should be much more challenging. In this context, the Pd catalyst based on L showed an excellent catalytic activity in the SM cross couplings of water-insoluble heteroaryl halides in pure water at room temperature. As showed in Table 3, the benzofuran, chromene and thiophene derivatives could be efficiently cross-coupled to form the desired products in high vields (Table 3, entries 1-3). Although N-heteroaryl halides have proven to be difficult substrates in the Pd-catalyzed C-C couplings,¹⁴ our method worked very well for a variety of such substrates including the pyridine, benzothiazole, quinoline and indole (with a free NH bond) derivatives (Table 3, entries 4-10). Also, it is interesting to note that 2-amino-5-bromopyridine, which is one of the most intractable among these substrates due to its competitive binding with Pd center, ^{14a,15} reacted in good yield with phenylboronic acid (Table 3, entry 6). Thus, this Pd catalytic system using L as ligand provides a highly stable and efficient catalyst for the SM reactions of heteroaryl substrates.



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Entry	Heteroaryl halide	Time (h)	Product (Yield ^b)
1	Br	8	
	÷		2a (91 %)
2	Ph O COOMe	9	Ph COOMe 2b (90 %)
3	OHC S Br	6	OHC S
4	MeOOC-	10	MeOOC
5	BrBr	6	Br
6	H ₂ NBr	8	H ₂ N
7	S N	10	S 2g (81 %)
8	Br	6	S N 2h (92 %)
9	Br	10	2i (87 %)
10	Br H	10	CH ₃

2j (88 %) a Conditions: the halide (1.0 mmol), the boronic acid (1.5 mmol), Na₂CO₃ (2 mmol), Pd (0.15 mol-%)/L = 1:4. b Yield of the isolated product.

This catalytic system exhibited high regio-selectivity in the SM cross coupling reaction, as shown by the arylation of 2,5dibromopyridine at the C2 position (Table 3, entry 5). Given that its diarylation in a one-pot procedure has remained poorly documented,^{12,16} especially uncovered in water at room temperature, we preferred to iteratively diarylate this compound in one pot. As shown in Scheme 3, after the first SM cross coupling was complete, such diarylation was achieved directly by the second SM reaction in a one-pot manner, which led to isolation of the desired double-coupled product of 3a in a 61 % overall yield. Although two different arylboronic acids were used as substrates, only small amounts of homo-coupling

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products of 4,4'-bianisole (13 %) and biphenyl (4 %) were observed in such a one-pot, two-step reaction.



Scheme 3 The diarylation of 2, 5-dibromopyridine in one-pot

In summary, we have demonstrated that the novel Pd catalyst based on the bidentate phosphine-type zwitterionic surfactant as ligand is an efficient catalytic system for the SM cross couplings in pure water at room temperature. The scope of this method is broad with respect to both coupling partners, and includes the much more challenging water-insoluble heteroaryl halides as substrates. Furthermore, the potential of this catalytic system to perform the SM cross couplings on a preparative scale has been demonstrated by the gram-scale assembly of the fungicide intermediate. In addition, the method has successfully be used in one pot to the iterative diarylation of 2,5-dibromopyridine with high regio-selectivity.

The general procedure for the cross-coupled biaryls is as follows: PdCl₂ (0.27 mg, 1.5 μ mol, 0.15 mol %), L (4.6 mg, 6 μ mol) and 3 mL H₂O were mixed and heated at 80 °C for 5 min. After cooling to room temperature, the bromine/iodine (1.0 mmol), the boronic acid (1.5 mmol) and Na₂CO₃ (212 mg, 2 mmol) were added. The reaction mixture was stirred at room temperature until the coupling reaction reached. After extracted with EtOAc, dried over Na₂SO₄, and concentrated in vacuo, the product was obtained by purification with silica gel flash chromatography.

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Graphic Abstract



In situ-generated Pd catalyst with bidentate phosphine-type zwitterionic surfactant as ligand showed high catalytic activity in the Suzuki reactions.