## Efficient Pyrimidone-Promoted Palladium-Catalyzed Suzuki–Miyaura Cross-Coupling Reaction

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**Abstract:** An efficient Pd(OAc)<sub>2</sub>/orotic acid catalytic system has been developed for Suzuki–Miyaura cross-coupling reaction of halides with aryl- and vinylboronic acids. The use of pyrimidone as ligand makes this method useful and attractive for the synthesis of stilbenes and derivative compounds. An attractive feature of this method is the tolerance of functional groups in both substrates.

Keywords: Suzuki–Miyaura cross-coupling reaction, pyrimidones, vinylboronic acids, halides, stilbenes

The palladium-catalyzed Suzuki-Miyaura cross-coupling reaction represents one of the most important transformations in constructing the carbon-carbon bonds in organic synthesis.<sup>1</sup> Phosphine-based ligands are generally air-sensitive and expensive, which places significant limits on their synthetic applications. Therefore, new types of ligands, such as heterocyclic carbenes,<sup>2</sup> imine and amine palladacycles,<sup>3</sup> oxime palladacycles,<sup>4</sup> diazabutadienes,<sup>5</sup> 2-aryl-2-oxazolines<sup>6</sup> and simple amines,<sup>7</sup> as well as ligandless systems,8 have emerged for use in the Suzuki-Miyaura cross-coupling reaction. Weakly bound ligands tend to give high catalytic activity, but are unstable and decompose into inactive palladium black, while catalytic cycle is blocked by strongly bound ligands in complexes to give low catalytic activity.9 Thus, proper choice/design of ligands will play a crucial role to generate efficient catalysts in such reaction. Orotic acid is a key compound of pyrimidine bases of nucleic acids in living organisms, and is also an interesting ligand in pyrimidine ring. Although, the coordination sites with most potential are the protonated carboxyl group and its adjacent nitrogen, when they coordinate to metal ion, the complexation ability of the exocyclic carbonyl oxygen is greatly enhanced.<sup>10</sup> Herein we wish to report pyrimidone as novel and efficient ligand for palladium-catalyzed Suzuki-Miyaura cross-couplings of halides with aryl- and vinylboronic acids (Scheme 1). To our surprise, there are no reports for Suzuki-Miyaura cross-coupling reaction with pyrimidone as ligand.

To examine the efficiency of Pd(OAc)<sub>2</sub>/pyrimidone as a catalyst in the Suzuki–Miyaura cross-coupling reaction, a model coupling reaction of 4-bromoanisole and phenylboronic acid was initially tested. The results are summarized in Table 1. The results showed that these pyrimidones were effective ligands for the palladium-

*SYNLETT* 2012, 23, 1221–1224 Advanced online publication: 26.04.2012 DOI: 10.1055/s-0031-1290885; Art ID: ST-2012-W0111-L © Georg Thieme Verlag Stuttgart · New York catalyzed Suzuki–Miyaura reaction. In the absence of ligands, only a 42% yield of the cross-coupling product was isolated in the presence of 1.5 mol% of Pd(OAc)<sub>2</sub> and two equivalents of Cs<sub>2</sub>CO<sub>3</sub> in acetone at 80 °C (entry 1). The yield of the product increased sharply upon addition of pyrimidone ligand (entries 2–5). Among the pyrimidone ligands investigated, orotic acid (L1; Figure 1) was found to be the best one, which gave the coupling product in high yield (entry 2). The other ligands (L2–L4; Figure 1) showed moderate efficiency, which gave the coupling product in 34–85% yield (entries 3–5). The results were similar to the reported conclusions.<sup>10</sup>

$$R^{1}X + R^{2}B(OH)_{2} \xrightarrow{Pd(OAc)_{2}, L1} R^{1}-R^{2}$$

$$X = I, Br, CI$$

$$R^{1}-R^{2}$$

R<sup>1</sup>, R<sup>2</sup> = aryl, vinyl

Scheme 1 Suzuki–Miyaura cross-coupling reaction with pyrimidone as ligand



Figure 1 Ligands tested in this work

Preliminary studies showed that L1 was the best ligand for palladium-catalyzed Suzuki cross-coupling reaction. Other reaction parameters, such as solvents, bases, and reaction temperature, have also been tested. The cross-coupling reaction of 4-bromoanisole with phenylboronic acid was investigated under argon (Table 2). We first conducted the reaction in the presence of different loadings of Pd(OAc)<sub>2</sub>/L1, using Cs<sub>2</sub>CO<sub>3</sub> (2 equiv) as base, and acetone as solvent (entries 1-3). It was observed that, using 1.5 mol% of Pd(OAc)<sub>2</sub>, 3 mol% of L1, the desired 4-bromobiphenyl (3) was obtained in 96% yield (entry 2). Decreasing the amounts of catalyst and ligand was found to be detrimental to catalytic efficiency (entry 3). Subsequently, systems were tested using 1.5 mol% of different palladium sources (entries 4-7), but the desired product was formed in lower yields. The efficiency of Pd(OAc)<sub>2</sub>/L1 was also evaluated in the presence of different inorganic bases and Et<sub>3</sub>N, as well as in a different sol-

 Table 1
 Screening of the Ligands for the Suzuki Reaction of 4-Bromoanisole and Arylboronic Acid<sup>a</sup>

 $\sim$ 

Br OMe +	Pd(OAc) <sub>2</sub> , ligand 80 °C, acetone B(OH) <sub>2</sub> MeO	
Entry	Ligand	Yield (%) <sup>b</sup>
1	none	42
2	L1	96
3	L2	85
4	L3	65
5	L4	34

<sup>a</sup> Reaction conditions: Pd(OAc)<sub>2</sub> (1.5 mol%), ligand (3 mol%), 4-bromoanisole (0.5 mmol), phenylboronic acid (0.6 mmol), Cs<sub>2</sub>CO<sub>3</sub> (1.0 mmol), acetone (5.0 mL), 80 °C, 11 h under argon.
 <sup>b</sup> Isolated yield.

vent. However, in all cases, no improvement could be observed (entries 8–14).

The effectiveness of L1 as the ligand was further confirmed using various aryl chlorides and aryl boronic acids under the optimum reaction conditions in acetone with Cs<sub>2</sub>CO<sub>3</sub> (Table 3).<sup>11</sup> The electron-rich and electron-poor aryl chlorides were smoothly converted into the corresponding biphenyl compounds in high yields (entries 2, 4, 6 and 9). In the more sterically demanding coupling reaction of 2-chloro-1,4-dimethylbenzene with phenylboronic acid, the product was obtained in a moderate yield (entry 9). The reactions of various arylboronic acids with aryl chlorides were also examined (entries 1, 3, 5, 10 and 11). As can be seen from the data contained in Table 3, the reaction appeared to be sensitive to the substituents on the boronic acid. Results suggested that the reaction with both electron-deficient and electron-rich arylboronic acids proceeded with difficulty to afford the respective biaryls with a moderate yield, and both the rate and the yield of the reaction for electron-deficient boronic acids were higher than those for the electron-rich boronic acids. For example, 4-methoxyphenylboronic acid afforded the product in 58% yield after 18 hours; however, 4-acetylphenylboronic acid gave a 72% yield and needed 10 hours (entries 3 and 10).

As the next step of this work, we synthesized (E)-stilbenes from Pd(OAc)<sub>2</sub>/L1-catalyzed Suzuki–Miyaura cross-coupling reaction between aryl halides 1 and aryl- and vinylboronic acids 2. As shown in Table 4, a variety of aryl iodides and aryl bromides were subjected to the optimized palladium-catalyzed cross-coupling reaction conditions with vinylboronic acids to provide the stilbenes in moderate to high yields (entries 1–8). Noteworthy was that the configuration of vinylboronic acids had tremendous influence on the reaction activity; (E)-vinylboronic acids were found to favor the reaction. When using 4-iodoanisole and (E)-vinylboronic acids, the desired product was obtained 
 Table 2
 Optimization of the Cross-Coupling Reaction Promoted by Orotic Acid<sup>a</sup>

	OMe +		₽d], L1	$\sum$	
Br	la 2	>>> `B(OH) <sub>2</sub> 2a	MeO	3	
Entry	Pd (1.5 mol%)	Base	Solvent	Time (h)	Yield (%) <sup>b</sup>
1	Pd(OAc) <sub>2</sub>	Cs <sub>2</sub> CO <sub>3</sub>	acetone	10	96
2°	$Pd(OAc)_2$	Cs <sub>2</sub> CO <sub>3</sub>	acetone	12	81
3 <sup>d</sup>	$Pd(OAc)_2$	Cs <sub>2</sub> CO <sub>3</sub>	acetone	12	80
4	PdCl <sub>2</sub>	Cs <sub>2</sub> CO <sub>3</sub>	acetone	12	75
5	Pd <sub>2</sub> (dba) <sub>3</sub>	Cs <sub>2</sub> CO <sub>3</sub>	acetone	12	42
6	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	Cs <sub>2</sub> CO <sub>3</sub>	acetone	24	58
7	Pd/C	Cs <sub>2</sub> CO <sub>3</sub>	acetone	24	42
8	$Pd(OAc)_2$	K <sub>2</sub> CO <sub>3</sub>	acetone	12	57
9	$Pd(OAc)_2$	Et <sub>3</sub> N	acetone	24	49
10	$Pd(OAc)_2$	K <sub>3</sub> PO <sub>4</sub>	acetone	24	30
11	$Pd(OAc)_2$	Cs <sub>2</sub> CO <sub>3</sub>	H <sub>2</sub> O	10	20
12 <sup>e</sup>	$Pd(OAc)_2$	Cs <sub>2</sub> CO <sub>3</sub>	acetone-H <sub>2</sub> O	10	64
13	$Pd(OAc)_2$	Cs <sub>2</sub> CO <sub>3</sub>	EtOH	10	67
14	$Pd(OAc)_2$	Cs <sub>2</sub> CO <sub>3</sub>	1,4-dioxane	10	48

<sup>a</sup> Reaction conditions: <b>1a</b> (0.5 mmol), <b>2a</b> (0.6 mmol), [Pd] (1.5
mol%), ligand (3 mol%), base (1.0 mmol) and solvent (5.0 mL) at 8

°C under argon.

<sup>b</sup> Isolated yield.

<sup>c</sup> Pd(OAc)<sub>2</sub> (1 mol%) and L1 (2 mol%).

<sup>d</sup> Pd(OAc)<sub>2</sub> (0.1 mol%) and L1 (0.2 mol%) at 100 °C.

<sup>e</sup> Acetone–H<sub>2</sub>O (1:1; 2 mL).

in 90% and 82% yield (entries 1 and 2); even an orthosubstituted aryl iodide afforded the corresponding stilbene compound in high yield (entry 4). However no reaction occurred when (Z)-vinylboronic acid was utilized (entry 3). In addition, aryl-substituted (E)-vinylboronic acid coupled with inactive aryl bromides showed higher reactivity, while that substituted with alkyl gave poor yields (entries 5 and 6). Vinyl bromides were also tested as the coupling partners (entries 9–11). (E)-(2-Bromovinyl)benzene (11) coupled with boronic acids 2a and 2g afforded successfully the corresponding products in excellent yields, after a significantly increased reaction temperature and the loadings of Pd(OAc)<sub>2</sub>/L1 (entries 10 and 11). A blank reaction was studied to further confirm the role of ligand L1 in the reaction of aryl halides and vinylboronic acids (entry 12). As mentioned in Table 1, the reaction yield decreased considerably in the absence of L1.

		2	ſ	$\overline{\mathbf{R}^2}$
R <sup>1</sup>	+ $R^2 \frac{II}{I}$	$Pd(OAc)_2$ , L1, Cs <sub>2</sub> CO <sub>3</sub> 80 °C, acetone, Ar		
1	2 B(	R <sup>1</sup>	9	
Entry	Aryl chloride	ArB(OH) <sub>2</sub>	Time (h)	Yield (%) <sup>b</sup>
1	CICI	B(OH)2	20	61 (4)
	1b	2b		
2	MeO-CI	B(OH)2	16	74 ( <b>3</b> )
	1c	2a		
3	1b	MeO-B(OH)2	16	58 ( <b>3</b> )
		2a		
4	O <sub>2</sub> N-CI	2a	10	85 ( <b>5</b> )
	1d			
5	1b	F B(OH)2	12	68 ( <b>6</b> )
	0,	2d		
6	УС-	2a	10	87 ( <b>7</b> )
7	1e 1c	2a	17	68 ( <b>8</b> )
8		2a	18	71 <b>(4</b> )
	1f			
9	CI	2a	18	44 ( <b>9</b> )
	1g			
10	1b	B(OH) <sub>2</sub>	10	72(7)
		2e		
11	1b	O <sub>2</sub> N-B(OH) <sub>2</sub>	10	70 (5)
		2f		

 Table 3 Cross-Coupling of Aryl Chlorides with Boronic Acids<sup>a</sup>

1223

Efficient Pd(OAc)2/Orotic Acid Catalytic System

D1V		Pd(OAc) <sub>2</sub> , <b>L1</b>	D1 D2	
1	+ K B(OH) <sub>2</sub> Cs;	<sub>2</sub> CO <sub>3</sub> , acetone, 80 °C	к <i>-</i> к	
Entry	R <sup>1</sup> X	R <sup>2</sup> B(OH) <sub>2</sub>	Time (h)	Yield (%) <sup>b</sup>
1	MeO-	B(OH)2	10	90 ( <b>10</b> )
	1h	2g		
2°	1h	B(OH) <sub>2</sub>	14	82 (11)
3°	1h	211 	24	trace (12)
4		2g	20	82 ( <b>13</b> )
	1i			
5	1a	2g	30	78 (10)
6	1a	2h	48	28 (11)
7	O <sub>2</sub> N Br	2g	14	92 (14)
8	1j 1j Br	2h	14	90 (15)
9 <sup>d</sup>		2a	36	42 (16)
	1k			
10 <sup>c,d</sup>	Br	2a	30	84 (17)
	11			
11 <sup>c,d</sup>	11	2g	30	90 ( <b>18</b> )
12 <sup>e</sup>	1h	2g	24	34 (10)

<sup>a</sup> Reaction conditions: 1 (0.5 mmol), 2 (0.6 mmol), Pd(OAc)<sub>2</sub> (1.5 mol%), L1 (3 mol%) and Cs<sub>2</sub>CO<sub>3</sub> (1 mmol) in acetone at 80–85 °C under Ar.

<sup>b</sup> Isolated yield.

<sup>c</sup> The reaction was carried out at 100 °C.

<sup>d</sup> Reaction conditions: 1 (0.5 mmol), 2 (0.6 mmol),  $Pd(OAc)_2$  (3 mol%), L1 (6 mol%) and  $Cs_2CO_3$  (1 mmol) in acetone under Ar. <sup>e</sup> The reaction was carried out in the absence of L1.

gand makes this method useful and attractive for the synthesis of stilbenes and derivative compounds. An attractive feature of this method is the tolerance of functional groups in both substrates.

<sup>a</sup> Reaction conditions: <b>1</b> (0.5 mmol), <b>2</b> (0.6 mmol), Pd(OAc) <sub>2</sub> (1.5
mol%), L1 (3 mol%), Cs <sub>2</sub> CO <sub>3</sub> (1 mmol), and acetone (5.0 mL) at 80-
85 °C under argon.
<sup>b</sup> Isolated yield.

In summary, we have developed a general method for Suzuki–Miyaura cross-coupling reaction of halides with aryl- and vinylboronic acids. The use of pyrimidone as li-

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- (11) Typical Experimental Procedure for the Palladium-Catalyzed Suzuki–Miyaura Cross-Coupling Reaction: A mixture of aryl halide 1 (0.5 mmol), arylboronic acid 2 (0.6 mmol), PdCl<sub>2</sub> (0.0075 mmol), orotic acid (0.015 mmol), and acetone (5 mL) was stirred in a Schlenk tube at 80 °C under Ar for 10 h. Complete consumption of the starting material was monitored by TLC and GC–MS analysis. After the reaction was complete, the mixture was poured into EtOAc, washed with brine ( $3 \times 10$  mL), and extracted with EtOAc. The combined organic layers were dried over anhyd Na<sub>2</sub>SO<sub>4</sub> and evaporated under vacuum. The residue was purified by flash column chromatography (hexane or hexane–EtOAc) providing the desired coupled product **3** in 96% yield.

**4-Methoxybiphenyl (3)**:<sup>12</sup> white solid; mp 86.5–87.2 °C (lit. mp 86 °C). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.54 (t, *J* = 9.4 Hz, 4 H), 7.41 (t, *J* = 9.4 Hz, 2 H), 7.31 (t, *J* = 9.6 Hz, 1 H), 6.98 (d, *J* = 8.9 Hz, 2 H), 3.85 (s, 3 H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 159.1, 140.7, 133.7, 128.7, 128.1, 126.7, 126.6, 114.2, 55.3. LRMS (EI, 70 eV): *m/z* (%) = 186 (16) [M<sup>+</sup> + 2], 184 (100) [M<sup>+</sup>], 153 (45), 119 (25).

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