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2,2′-Diamino-6,6′-dimethylbiphenyl as an efficient ligand in the palladium-catalyzed Suzuki–Miyaura and Mizoroki–Heck reactions

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ABSTRACT

2,2′-Diamino-6,6′-dimethylbiphenyl was found to be an efficient ligand in the palladium-catalyzed Suzuki–Miyaura coupling reactions of aryl iodides, bromides, and chlorides and Mizoroki–Heck reactions of aryl iodides and bromides. Under appropriate conditions, all reactions gave the desired products in moderate to excellent yields. The ligand is inexpensive, air-stable and easy to available.

1. Introduction

Palladium-catalyzed cross-coupling reactions are versatile and efficient methods for carbon–carbon bond formations.[1] Among them, the Suzuki–Miyaura and Mizoroki–Heck coupling reactions play important roles in modern synthetic chemistry.[2,3] Improvement of these reactions is greatly relied on the reactivity of the palladium catalyst by using increasing efficient supporting ligands. To date, many efforts are made to the search for more efficient ligands. During the past decades, the most common ligands used for these two coupling reactions are phosphine-based ones.[4] Since most of the phosphine-based ligands are air and/or moisture-sensitive, in recent years, phosphine-free ligand as *N*-heterocyclic carbenes (NHCs) have also been employed.[5] In addition, alkyl-substituted diamines, such as ethylenediamines and cyclohexane-1,2-diamines, acting as versatile ligands, have been widely used in the transition-metal catalyzed carbon–carbon bonds and carbon–heteroatom bonds formations during the last years.[6,7] As part of our ongoing research toward effective ligands for transition-metal catalyzed cross-coupling reactions for carbon–carbon bond formations, it was found that easily available 2,2′-diamino-6,6′-dimethylbiphenyl (L1),[8] is a useful ligand for the palladium-catalyzed Suzuki–Miyaura coupling reactions of aryl halides including iodides, bromides, and chlorides and Mizoroki–Heck reactions of aryl iodides and bromides. Herein, we wish to report these results in detail.

2. Results and discussion

In initial investigations, we examined the Suzuki–Miyaura coupling reaction of the model substrate 4-methoxyphenyl iodide (**1a**) with 4-methylphenylboronic acid (**2a**), using 2,2′-diamino-6,6′-dimethylbiphenyl (L1) (10 mol %) (Scheme 1) as the ligand and $Pd(OAc)_2$ (5 mol %) as the catalyst in THF at room temperature for 48 h (Table 1). As can be seen from Table 1, of the bases screened, Cs_2CO_3 showed the best result and the corresponding coupling product **3a** was obtained in 90% yield (Table 1, entry 5). For the other solvents as toluene, CH_2Cl_2, dioxane, DCE, and CH_3CN, all showed inferior results compared to that of THF (Table 1, entries 8–12). When L1 was replaced by other analogues as L2,[9] L3,[10] L4,[11] L5,[12] and L6,[12] inferior results were found (Table 1, entries 13–17). Finally, it was found that if the reaction temperature was elevated to 40 °C, the corresponding reactions can be finished within 12 h with 96% yield using L1 as the ligand (Table 1, entry 18).

Thus, the optimal reaction conditions are using $Pd(OAc)_2$ (5 mol %) as the catalyst, L1 (10 mol %) as the ligand, Cs_2CO_3 (2.0 equiv) as the base and THF (2.0 mL) as the solvent at the temperature of 40 °C.

With the optimal reaction conditions in hand, we firstly explored the scope and limitations of the reaction with a set of aryl

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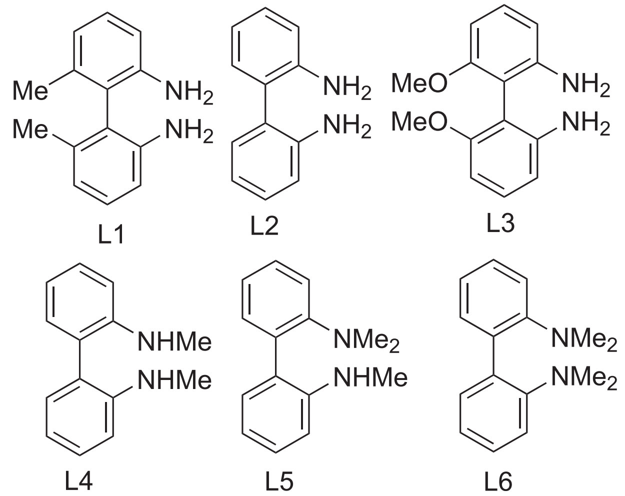
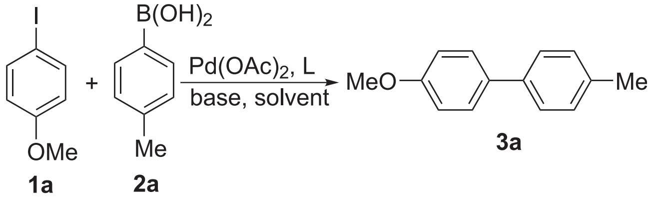


Scheme 1. Ligands screened.

iodides and arylboronic acids. We were pleased to find out that all reactions afforded the desired coupling products **3** in high yields within 12 h and substituents, either electron-donating group as methoxy group or electron-withdrawing group as Cl atom on the phenyl ring of **1** have almost no significant effect on these reactions (Table 2, entries 1–3). 2-Thiophenyl iodide **1d** also led to the corresponding coupling product **3d** in high yield (Table 2, entry 4). Nevertheless, to our disappointment, when arylbromide as 4-methoxyphenyl bromide **1e** was used as the substrate, almost no desired product was obtained under the optimal reaction conditions (Table 2, entry 5). Gratifyingly, when the reaction temperature was elevated to 70 °C, consistent with the above studies, the reactions of aryl bromides **1** with arylboronic acids **2** also took place smoothly to give the corresponding products **3** in moderate to high yields (Table 2, entries 6–13). Substituents on the phenyl rings of aryl bromides and arylboronic acids have little effect on the reaction. For instance, the reaction of 3-methoxyphenyl bromide **1f** with 4-chlorophenylboronic acid **2d** only gave the coupling product **3g** in 72% yield (Table 2, entry 11). It is worthy of noting that at this temperature (70 °C), Cl atom on the phenyl ring kept untouched (Table 2, entries 8 and 11).

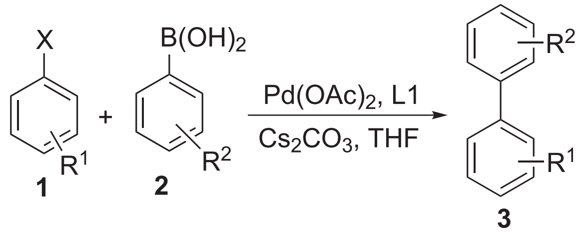
Table 1
Optimization for the reaction conditions of **1a** with **2a**

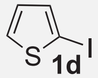


Entry[a]	Ligand	Base	Solvent	Yield (%)[b]
1	L1	NaOH	THF	10
2	L1	KOH	THF	82
3	L1	CH_3COOK	THF	9
4	L1	$KHCO_3$	THF	3
5	L1	Cs_2CO_3	THF	90
6	L1	Na_2CO_3	THF	15
7	L1	K_2CO_3	THF	24
8	L1	Cs_2CO_3	Toluene	48
9	L1	Cs_2CO_3	CH_2Cl_2	36
10	L1	Cs_2CO_3	Dioxane	73
11	L1	Cs_2CO_3	DCE	24
12	L1	Cs_2CO_3	CH_3CN	76
13	L2	Cs_2CO_3	THF	10
14	L3	Cs_2CO_3	THF	14
15	L4	Cs_2CO_3	THF	63
16	L5	Cs_2CO_3	THF	79
17	L6	Cs_2CO_3	THF	74
18[c]	L1	Cs_2CO_3	THF	96

[a] Otherwise specified, all reactions were carried out using **1a** (0.5 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (5 mol %), ligand (10 mol %), and base (2.0 equiv) in solvent (2.0 mL) at rt for 48 h.
[b] Isolated yields.
[c] The reaction was carried out at 40 °C for 12 h.

Table 2
$Pd(OAc)_2$-catalyzed Suzuki–Miyaura coupling reaction of **1** with **2**



Entry[a]	**1** (R^1/X)	**2** (R^2)	Yield[b] (%)
1	**1a** (4-MeO/I)	**2b** (H)	**3b** (86)
2	**1b** (4-Cl/I)	**2c** (4-MeO)	**3c** (92)
3	**1c** (H/I)	**2c**	**3b** (92)
4	 **1d**	**2c**	**3d** (95)
5[c]	**1e** (4-MeO/Br)	**2b**	Trace
6	**1e**	**2b**	**3b** (95)
7	**1e**	**2a** (4-Me)	**3a** (91)
8	**1e**	**2d** (4-Cl)	**3c** (75)
9	**1e**	**2e** (3,5-Me, Me)	**3e** (94)
10	**1f** (3-MeO/Br)	**2b**	**3f** (94)
11	**1f**	**2d**	**3g** (72)
12	**1g** (4-F/Br)	**2c**	**3h** (90)
13	**1h** (H/Br)	**2c**	**3b** (94)

[a] Otherwise specified, all reactions were carried out using **1** (0.5 mmol), **2** (0.6 mmol), $Pd(OAc)_2$ (5 mol %), L1 (10 mol %), and Cs_2CO_3 (1.0 mmol) in THF (2.0 mL) at 40 °C for 12 h (for iodides) or 70 °C for 24 h (for bromides).
[b] Isolated yields.
[c] The reaction was carried out at 40 °C.

It is known to all that despite the lower reactivity of aryl chlorides comparable to the common partners as organic bromides, iodides, and triflates, chlorides are arguably the most useful single class of substrates, because of their lower cost and the wider diversity of available compounds.[13] Encouraged by the success on the palladium-catalyzed Suzuki–Miyaura coupling reactions of aryl iodides and bromides with arylboronic acids using 2,2′-diamino-6,6′-dimethylbiphenyl (L1) as the ligand, we then turned our interests to the reactions of aryl chlorides. Optimization procedure was carried out using 4-methoxyphenyl chloride **1i** (0.5 mmol) and phenylboronic acid **2b** (0.75 mmol) as the substrates, $Pd(OAc)_2$ (5 mol %) as the catalyst, L1 (10 mol %) as the ligand, Cs_2CO_3 (2.0 equiv) as the base and DMF as the solvent. The results are shown in Table 3. After several trials and errors, to our delight, it was found that the best result can be obtained using 1.0 mL DMF as the solvent at 110 °C and the corresponding coupling product **3b** was obtained in 75% yield (Table 3, entry 2). In other solvents as toluene and DMSO, only very lower yield or no product was obtained for the same reaction (Table 3, entries 5 and 6).

Under the reaction conditions using $Pd(OAc)_2$ (5 mol %) as the catalyst, L1 (10 mol %) as the ligand, Cs_2CO_3 (2.0 equiv) as the base and DMF (1.0 mL) as the solvent at 110 °C, a variety of aryl chlorides and arylboronic acids were examined (Table 4). All the substituted aryl chlorides tested afforded the corresponding products **3** in moderate to good yields. Substituents on the phenyl ring of chlorides slightly affected the reaction and electron-withdrawing group on the phenyl ring of aryl chloride gave better result (Table 4, entries 1 vs 3).