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Efficient pyridylbenzamidine ligands for palladium-catalyzed Suzuki–Miyaura reaction

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A series of pyridylbenzamidine ligands were applied in palladium-catalyzed Suzuki–Miyaura reactions and the effect of ligand on catalytic properties was evaluated. Under the optimization conditions, the bulky and electron-donating nitrogen donor ligands were successfully used to catalyze the reaction of a variety of aryl bromides and aryl chlorides with arylboronic acid, giving the desired products in moderate to high yields. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: Suzuki–Miyaura reaction; pyridylbenzamidine ligand; aryl bromide; aryl chloride

Introduction

Palladium-catalyzed cross-coupling reactions are now widely recognized as the most versatile tools for carbon–carbon bond formation and are widely used in organic synthesis.[1–21] In 2010, the Nobel Prize for Chemistry was awarded to R. F. Heck, Ei-ichi Negishi and A. Suzuki, who have achieved excellent progress in this field.[22] Among the palladium-catalyzed cross-coupling reactions, the Suzuki–Miyaura reaction is now becoming a very powerful tool in synthetic methodologies, particularly for convenient formation of biaryl compounds, owing to the high stability and wide range of functional group tolerance of the reactants and products. Many palladium complexes have been used to promote the Suzuki–Miyaura cross-coupling reaction, while phosphine ligands have commonly proved to be very efficient and allowed the use of sterically hindered aryl bromide substrates and even aryl chlorides at low catalyst loadings and relatively low reaction temperatures.[23–29] However, these phosphine ligands are often sensitive to air and moisture, and require air-free handling in order to minimize ligand oxidation, limiting their further practical utilization. Therefore, phosphine-free ligands have attracted great attention in recent years.[30–42]

It is a trend that phosphine-free ligands which are easily available, and are moisture and air stable, are in heavy demand in the palladium-catalyzed Suzuki–Miyaura reactions of aryl halides with arylboronic acids. In particular, nitrogen donor ligands and their palladium complexes have shown excellent catalytic activity because of their strong σ-donating abilities.[43] For example, Kirchner and co-workers found that the β-diimine ligands exhibited moderate activity towards aryl bromides.[44] A family of benzimidazolium–pyrazole palladium complexes developed by Andy Hor turned out to be excellent for Suzuki–Miyaura reaction and other types of cross-coupling reactions under homogeneous conditions.[45] Moreover, nitrogen ligands bearing pyridine as a strong coordination donor and labile group gave superior catalytic performance in other carbon–carbon- and carbon–nitrogen-forming reactions.[46–59] Generally, aryl bromides are usually employed as coupling substrates in the above protocols. However, the more inexpensive aryl chlorides have been rarely used as coupling partners because the activation of aryl chlorides is much more difficult than aryl bromides and iodides. To search for new catalysts that exhibit high activity and stability with a broad range of substrates in the coupling reaction, as part of our ongoing research interest in cross-coupling with phosphine-free ligands,[60–62] we herein report a series of pyridylbenzamidine ligands (Fig. 1) as phosphine-free ligands for Suzuki–Miyaura reaction under aerobic conditions.

Experimental

Materials and Methods

All the chemical reagents (AR grade) were purchased from commercial resources and used without further purification. NMR spectra were recorded on a Bruker 300 MHz spectrometer using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard. Mass spectral data were recorded on an Acquity UPLC-Q-Tof Micro MS detector. Elemental analysis was done using a Vario EL III instrument (Elementar Analysen Systeme Gmbh, Germany).

The X-ray diffraction data of the single crystal of **L3PdCl$_2$** was obtained with ω-2θ scan mode on a Bruker SMART 1000 CCD diffractiometer with graphite-monochromated Mo $K\alpha$ radiation ($\lambda = 0.71073$) at 110 K. The structure was solved using direct methods, and refinement with full-matrix least squares on F^2 was performed with the SHELXTL program package.[63] The absolute structure was determined based on differences in Friedel pairs included in the dataset. All non-hydrogen atoms were refined anisotropically. The data collection and structure refinement parameters are summarized in Table 1.

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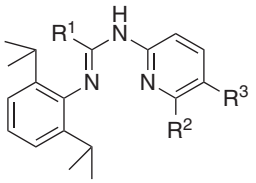


L1: R^1=Ph, R^2=H, R^3=H;
L2: R^1=p-$CH_3OC_6H_4$, R^2=H, R^3=H;
L3: R^1=p-$CH_3C_6H_4$, R^2=H, R^3=H;
L4: R^1=Ph, R^2=H, R^3=NO_2;
L5: R^1=p-$CH_3C_6H_4$, R^2=CH_3, R^3=H;
L6: R^1=Ph, R^2=CH_3, R^3=H;

Figure 1. Structure of pyridylbenzamidine ligands.

Table 1. Crystallographic data for **L3PdCl$_2$**

Complex	L3PdCl$_2$
Formula	$C_{25}H_{29}Cl_2N_3Pd$
Formula weight	548.81
Crystal color; Form	Yellow block
Crystal size (mm)	0.15 × 0.15 × 0.24
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
T (K)	110 (2)
a(Å)	12.6883(19)
b(Å)	13.254(2)
c(Å)	14.200(2)
V(Å^3)	2388.0(6)
D_{calc} (mg m^{-3})	1.526
F (000)	1120
Z	4
μ(mm^{-1})	1.018
θ range for data collection (°)	2.1 – 27.1
Reflections collected	12 123
R_{int}	0.034
Data/ parameters	5174/297
Goodness-of-fit	1.07
$R_1/wR_2[I>2\sigma(I)]$	0.030/0.059
R_1/wR_2(all data)	0.039/0.062

2,6-i$Pr_2C_6H_3$-;N-;C(Ph)-;NH-;Py (**L1**), 2,6-i$Pr_2C_6H_3$-;N ;C(4-$CH_3OC_6H_4$)-;NH-;Py (**L2**), 2,6-i$Pr_2C_6H_3$-;N ;C(4-$CH_3C_6H_4$)-;NH-;(4-NO_2-;Py) (**L4**) and 2,6-i$Pr_2C_6H_3$-;N ;C(4-$CH_3C_6H_4$)-;NH-;(5-CH_3-;Py) (**L5**) were synthesized according to our previous reports.[64,65]

General Procedure for the Synthesis of Ligand and Palladium Complex

*Synthesis of 2,6-i$Pr_2C_6H_3$-;N ;C(4-$CH_3C_6H_4$)-;NH-;Py (**L3**)*

p-Toluoyl chloride (1.33 ml, 10 mmol) was slowly added to a vigorously stirred solution of 2,6-diisopropylaniline (1.9 ml, 10 mmol) in CH_2Cl_2 (45 ml), then triethylamine (1.6 ml, 11 mmol) was added in one portion and a white precipitate appeared immediately. After refluxing for 3 h, the precipitate of $(C_2H_5)_3N$.HCl was filtrated, and a white solid powder of amide was obtained by evaporating the solvent. Then excess of thionyl chloride (2.0 ml, 28 mmol) was added to the amide and the reaction mixtures were stirred for 2 h at 80°C. The remaining thionyl chloride was distilled off under reduced pressure to give the imidoyl chloride as a yellow and slowly solidifying oil. Successively, toluene (40 ml), triethylamine (1.6 ml, 11 mmol) and 2-aminopyridine (0.94 g, 10 mmol) were added to the reaction system. The mixtures were heated to reflux for 24 h under the protection of nitrogen atmosphere. $(C_2H_5)_3N$.HCl was removed by filtration and toluene was evaporated from the filtrate. After recrystallization of the product from ethanol, 2,6-i$Pr_2C_6H_3$-;N ;C(4-$CH_3C_6H_4$)-;NH-;Py (**L3**) was obtained as light-yellow crystals. Yield 45%; m.p. 165°C. EI-MS (*m/z*) 372 $[M]^+$; 279 $[M-C_5H_5N_2]^+$.^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.95 (br, 1H, pyridyl α-H), 7.57–6.78 (m, 10H, pyridyl and phenyl protons), 2.99 (m, 2H, C*H*$(CH_3)_2$), 2.47 (s, 3H, CH_3), 0.96 (d, *J* = 6.9 Hz, 12H, CH$(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 166.74 (*C* ;N), 157.78 (2-C_{py}), 146.22 (6-C_{py}), 143.95 (C_{Ar}-;N), 136.91(4-C_{py}), 134.49 (C_{Ar}-;CH_3), 131.64 (C_{Ar}-;$CH(CH_3)_2$), 129.15 (C_{Ar}), 128.69 (C_{Ar}), 127.59 (C_{Ar}), 127.05 (C_{Ar}), 123.43 (5-C_{py}), 122.61(3-C_{py}), 27.98 ($CH(CH_3)_2$), 24.11 ($CH(CH_3)_2$), 22.49 (C_{Ar}-;CH_3).

*Synthesis of 2,6-i$Pr_2C_6H_3$-;N ;C(Ph)-;NH-;(5-CH_3-;Py) (**L6**)*

2,6-i$Pr_2C_6H_3$-;N ;C(4-$CH_3C_6H_4$)-;NH-(5-;CH_3-;Py) (**L6**) was synthesized according to the method described above as light-yellow crystals. Yield 68%; m.p. 166°C.^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm) [isomer ratio of 4.9:1] major isomer: 7.95 (br, 1H, pyridyl α-H), 7.57–6.78 (m, 10H, pyridyl and phenyl protons), 2.99 (m, 2H, C*H*$(CH_3)_2$), 2.47 (s, 3H, CH_3), 0.96 (d, *J* = 6.9 Hz, 12H, CH$(CH_3)_2$). Minor isomer: 7.95 (br, 1H, pyridyl a-H), 7.66–6.92 (m, 10H, pyridyl and phenyl protons), 3.16 (m, 2H, C*H*$(CH_3)_2$), 2.47 (s, 3H, CH_3), 1.26 (d, *J* = 6.9 Hz, 12H, CH$(CH_3)_2$). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm) major isomer: 166.74 (*C* ;N), 157.78 (2-C_{py}), 146.22 (6-C_{py}), 143.95 (C_{Ar}-;N), 136.91(4-C_{py}), 134.49 (C_{Ar}-;CH_3), 131.64 (C_{Ar}-;$CH(CH_3)_2$), 129.15 (C_{Ar}), 128.69 (C_{Ar}), 127.59 (C_{Ar}), 127.05 (C_{Ar}), 123.43 (5-C_{py}), 122.61(3-C_{py}), 27.98 ($CH(CH_3)_2$), 24.11($CH(CH_3)_2$), 22.49 (C_{Ar}-;CH_3). Minor isomer: 166.74 (*C* ;N), 157.78 (2-C_{py}), 146.22 (6-C_{py}), 143.95 (C_{Ar}-;N), 136.91 (4-C_{py}), 134.49 (C_{Ar}-;CH_3), 131.64 (C_{Ar}-;$CH(CH_3)_2$), 129.15 (C_{Ar}), 128.69 (C_{Ar}), 127.59 (C_{Ar}), 127.05 (C_{Ar}), 123.43 (5-C_{py}), 122.61(3-C_{py}), 29.03 ($CH(CH_3)_2$), 24.42 ($CH(CH_3)_2$), 22.58 (C_{Ar}-;CH_3). EI-MS (*m/z*): 372 $[M]^+$; 265 $[M-C_6H_8N_2]^+$. Elemental anal. Calc. for $C_{25}H_{29}N_3$: C, 80.82; H, 7.87; N, 11.31. Found: C, 80.77; H, 7.82; N, 11.24%.

*Synthesis of [2,6-i$Pr_2C_6H_3$-;N ;C(4-$CH_3C_6H_4$)-;NH-;Py]$PdCl_2$ (**L3PdCl$_2$**)*

A suspension of $PdCl_2$ (177 mg, 1 mmol) in acetonitrile (20 ml) was refluxed until a clear solution of $Pd(MeCN)_2Cl_2$ was formed. When cooling to room temperature, **L3** (371 mg, 1.0 mmol) was then added and stirred for another 12 h. After the solvent was concentrated to ~5 ml, 20 ml hexane was added and an orange solid was obtained. Washed with hexane (2 × 10 ml) and dried under vacuum, the orange palladium complex was received in 96% yield; m.p. 288°C. ESI-MS (*m/z*): $[M+Na]^+$ 571;$[M-Cl]^+$ 514; $[M-2Cl]^+$ 476, 479, 474. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 9.56 (s, 1H, pyridyl α-H), 8.33–6.02 (m, 10H, pyridyl and phenyl protons), 2.87 (m, 2H, C*H*$(CH_3)_2$), 2.32 (s, 3H, C*H*$_3$), 1.03(d, *J* = 6.7 Hz, 12H, CH(C*H*$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 163.81 (*C* ;N), 149.68 (2-C_{py}), 145.85 (6-C_{py}), 140.52 (C_{Ar}-;N), 138.19 (4-C_{py}), 133.52 (C_{Ar}-;CH_3), 129.68 (C_{Ar}-;$CH(CH_3)_2$), 129.30 (C_{Ar}), 128.88 (C_{Ar}), 127.53 (C_{Ar}), 123.54 (C_{Ar}), 123.10 (C_{Ar}), 119.01 (5-C_{py}), 116.96 (3-C_{py}), 28.34 ($CH(CH_3)_2$), 25.42 ($CH(CH_3)_2$), 22.68 (C_{Ar}-;CH_3). Elemental anal. Calc. for $C_{25}H_{29}Cl_2N_3Pd$: C, 54.71; H, 5.33; N, 7.66. Found. C: 54.63; H, 5.26; N, 7.51.

General Procedure for Suzuki–Miyaura Reaction

In a round-bottom bottle, ligand (1% mmol), $PdCl_2$ (1% mmol), aryl halides (1 mmol), arylboronic acid (1.2 mmol), K_2CO_3 (2 mmol) and 5 ml solvent were added with a magnetic stir bar. The reactants were heated to the required temperature for the described time. Then the solvent was removed under reduced pressure. The residue was diluted with EtOAc (5 ml), followed by extraction twice (2 × 5 ml) with EtOAc. The organic layer was combined and dried

with anhydrous Na_2SO_4, filtered and evaporated under vacuum. The isolated products were purified by silica-gel column chromatography using petroleum/ethyl acetate as an eluent. All the isolated desired biaryl products were characterized by ^1H and ^{13}C NMR and comparison of the melting points with the literature data.

Results and Discussion

Synthesis and characterization of palladium complex

The pyridylbenzamidine ligands were easily prepared in moderate yield. Moreover, reaction of **L3** with $Pd(MeCN)_2Cl_2$ afforded the corresponding **L3PdCl$_2$** in high yield. A great advantage of the described palladium complex is that it is a thermally robust orange solid that is stable towards air both in the solid state and in solution. It can therefore be exposed to air without decomposition. A single crystal of the complex suitable for X-ray diffraction was grown from CH_2Cl_2/hexane solution at ambient temperature. A diagram of the molecular structure is presented in Fig. 2 along with selected bond lengths and bond angles. As seen from Fig. 2, the expected complex shows the formation of a six-membered chelate ring with a proton at the central nitrogen atom; the palladium center adopts a slightly distorted square planar coordination geometry (the sum of the angles around the palladium atom is ~362°). The C6–N3 and C5–N3 bond lengths are 1.378(4) and 1.392(4) Å, respectively. This is similar to typical C(sp^2)–N(sp^2) single and double bond lengths, which indicates rather significant delocalization in the complex. Similar to the related Pd(II) 1,2,4-triphenyl-1,3,5-triazapentadiene complexes,[66] the six-membered chelate ring of **L3PdCl$_2$** is not exactly planar but distorted in a boat conformation. Moreover, the aryl ring on the aniline moiety is approximately perpendicular to the chelate ring, with a dihedral angle of ~86°, which can be explained by steric repulsion of the bulky substituted 2,6-diisopropyl group on the aniline and *p*-toluoyl backbone, and thus will provide effective protection of the metal center in the cross-coupling.

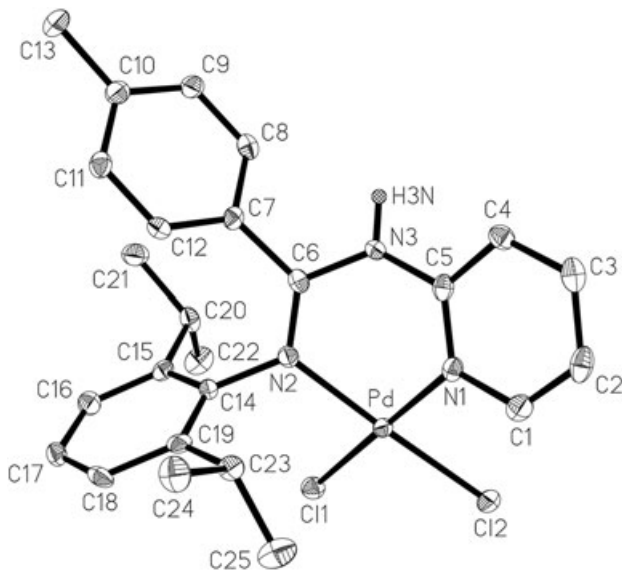


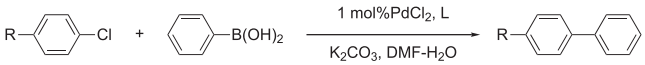
Figure 2. Molecular structure of **L3PdCl$_2$** depicted with 50% displacement ellipsoids and with carbon-bound hydrogen atoms omitted. Selected bond lengths (Å) and angles (°): C6–N3 1.378(4), C5–N3 1.392(4), C6–N2 1.288(4), C5–N1 1.337(4), Pd–N1 2.021(2), Pd–N2 2.050(2), Pd–Cl1 2.2993(8), Pd–Cl2 2.3031(8), N1–Pd–N2 88.10(9), N1–Pd–Cl1 178.62(7), N1–Pd–Cl2 91.13(7), N2–Pd–Cl1 92.85(7), N2–Pd–Cl2 (2) 177.80(7), Cl1–Pd–Cl2 87.87(3).

Suzuki–Miyaura Cross-Coupling of Aryl Halides with Arylboronic Acids

In order to investigate the activity of the pyridylbenzamidine ligands (**L1–6**), 4-chlorobenzonitrile and phenylboronic acid were selected as coupling partners in the presence of 1 mol% ligand and 1 mol% $PdCl_2$ in the model reaction (Table 2). The experiments were carried out under aerobic conditions at 110°C for 4 h utilizing K_2CO_3 as a base in DMF/H_2O.

As illustrated in Table 2, the steric and electronic substituents on the ligand played an important role in catalytic ability. Among the ligands investigated, **L1**, with the phenyl group on R^1, showed moderate efficiency and provided the coupling product in 79% yield (Table 2, run 1). Meanwhile, **L2** and **L3**, with an anisole and *p*-toluoyl group on R^1, were found to be more efficient ligands and afforded the coupling product in 86% and 84% yield, respectively (Table 2, runs 2 and 3). The results suggested that the increase in the electron-donating properties of the ligand would lead to an increase in the rate of oxidative addition and stabilization of the palladium species; even these substituents were far away from the coordinated imine nitrogen atom. Comparatively, **L4**, with an electron-withdrawing nitro group on the pyridyl ring in the R^3 position, was much less active under the same conditions (67% yield), which indicated that the decreased electron density of the pyridyl ring caused by the nitro group might lead to the instability and low catalytic activity of the *in situ* formed palladium complex. Besides the electronic effect, the steric properties of the substituents on the ligand also exhibited a profound effect on catalytic activity. For instance, **L5** and **L6**, with the methyl group in the R^2 position, which is adjacent to the coordinated pyridyl nitrogen

Table 2. Ligand screening on Suzuki–Miyaura cross-coupling reaction



Run	R	L or $LPdCl_2$	Pd (mol%)[a]	T (°C)	t (h)	Yield (%)[a]
1	CN	L1	1	110	4	79
2	CN	L2	1	110	4	86
3	CN	L3	1	110	4	84
4[b]	CN	$L3PdCl_2$	1	110	4	85
5	CN	L4	1	110	4	67
6	CN	L5	1	110	4	90
7	CN	L6	1	110	4	92
8	CN	None	1	110	4	82
9	CHO	L1	1	110	6	48
10	CHO	L2	1	110	6	56
11	CHO	L3	1	110	6	51
12[b]	CHO	$L3PdCl_2$	1	110	6	57
13	CHO	L4	1	110	6	44
14	CHO	L5	1	110	6	78
15	CHO	L6	1	110	6	85
16	CHO	None	1	110	6	79

Reaction conditions: 4-Chloronitrobenzene (1 mmol), phenylboronic acid (1.2 mmol), K_2CO_3 (2.0 mmol), DMF: H_2O=4ml: 1 ml, reaction time is 6 hours, under aerobic atmosphere. The molar ratio of Ligand and Pd is 1:1.

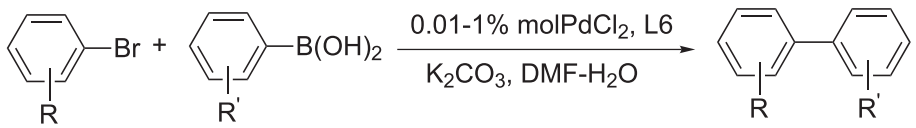
[a]Isolated yield.

[b]The palladium complex is used.

atom, showed the corresponding biphenyls in 90% and 92% yield, respectively (Table 2, runs 6 and 7). Apparently, the increased steric bulk on the ligands facilitates the reductive elimination process in the catalytic cycle.[67] It is noteworthy that the palladium complex of **L3PdCl$_2$** was also effective for this cross-coupling reaction, giving a product of 85% yield (Table 2, run 4), which was comparative to the case of *in situ* complex formation (Table 2, run 3). To further reveal the role of the pyridylbenzamidine ligands to promote the reaction, cross-coupling was conducted in the absence of ligands for comparison. The result showed that a moderate yield of 82% was obtained in the presence of 1 mol% of $PdCl_2$, which was much less than that of **L6**/$PdCl_2$ system (Table 2, run 8). Moreover, the catalytic properties of these ligands were explored by screening another reaction between 4-chlorobenzaldehyde and phenylboronic acid. The results provided guidelines showing that **L6** was the best choice for the coupling (Table 2, runs 9–16).

Based on the ligand screening, **L6** was chosen as the most effective ligand in the following Suzuki–Miyaura cross-coupling reactions of different aryl halides with arylboronic acids. With the optimal reaction conditions in hand, we checked the scope of the aryl bromides by conducting a series of experiments. As seen from Table 3, the activated 4-bromonitrobenzene was coupled smoothly with phenylboronic acid in only 0.5 h, giving the corresponding product in almost a quantitative yield of 98% at room temperature under aerobic conditions (Table 3, run 1). However, 4-bromochlorobenzene just delivered its coupling product in a lower yield of 76% at room temperature (Table 3, run 2). Meanwhile, reduced yields were also observed with other unactivated electron-rich aryl bromide under the same reaction conditions (Table 3, runs 3–5). To our delight, as the temperature increased to 60°C, most of the substrates including activated and deactivated aryl bromides were all successfully transformed to the desired products in quantitative yields within 2 h. For instance, 4-bromoanisole gave its product in 95% yield (Table 3, run 11). The more hindered electronic candidates, such as 1-bromonaphthalene, 2-bromoaniline and 2-bromotoluene, also produced satisfactory yields (Table 3, runs 13–15). However, the bulky substituted 2-bromomesitylene gave a much lower yield of 48% at 60°C in 24 h due to its steric hindrance and low reactivity (Table 3, run 19).

Table 3. Suzuki–Miyaura cros s-coupling reaction of aryl bromides with arylboronic acid



Run	Ar-;Br	$ArB(OH)_2$	Product	Pd (mol%)	*T* (°C)	*t* (h)	Yield (%)[a]
1	4-O_2NPhBr	$PhB(OH)_2$	4-O_2NPh-;Ph	1	RT	0.5	98
2	4-ClPhBr	$PhB(OH)_2$	4-ClPh-;Ph	1	RT	4	76
3	4-CH_3PhBr	$PhB(OH)_2$	4-CH_3Ph-;Ph	1	RT	6	64
4	4–CH_3OPhBr	$PhB(OH)_2$	4-CH_3OPh-;Ph	1	RT	4	60
5	NaphtylBr	$PhB(OH)_2$	Naphtyl-;Ph	1	RT	6	61
6	4-ClPhBr	$PhB(OH)_2$	4-ClPh-;Ph	1	60	2	98
7	4-CH_3PhBr	$PhB(OH)_2$	4-CH_3Ph-;Ph	1	60	2	97
8	4-CH_3PhBr	$PhB(OH)_2$	4-CH_3Ph-;Ph	0.5	60	2	94
9	4-CH_3PhBr	$PhB(OH)_2$	4-CH_3Ph-;Ph	0.1	60	2	90
10	4-CH_3PhBr	$PhB(OH)_2$	4-CH_3Ph-;Ph	0.01	60	2	18
11	4-CH_3OPhBr	$PhB(OH)_2$	4-CH_3OPh-;Ph	1	60	2	95
12	4-^{t}BuPhBr	$PhB(OH)_2$	4-^{t}BuPh-;Ph	1	60	4	80
13	NaphtylBr	$PhB(OH)_2$	Naphtyl-;Ph	1	60	2	99
14[b]	2-NH_2PhBr	$PhB(OH)_2$	2-NH_2Ph-;Ph	1	60	4	80
15	2-CH_3PhBr	$PhB(OH)_2$	2-CH_3Ph-;Ph	1	60	2	96
16	2-CH_3PhBr	$PhB(OH)_2$	2-CH_3Ph-;Ph	0.5	60	2	92
17	2-CH_3PhBr	$PhB(OH)_2$	2-CH_3Ph-;Ph	0.1	60	2	20
18	2-CH_3PhBr	$PhB(OH)_2$	2-CH_3Ph-;Ph	0.01	60	2	5
19	2,4,6-trimethylphBr	$PhB(OH)_2$	2,4,6-trimethylph-;Ph	1	60	24	48
20	4-CH_3OPhBr	2-CH_3PhB$(OH)_2$	4-CH_3Oph-;2′-CH3Ph	1	60	2	98
21	4-^{t}BuPhBr	2-CH_3PhB$(OH)_2$	4-^{t}BuPh-;2′-CH_3Ph	1	90	2	99
22	4-CH_3PhBr	4-ClPhb$(OH)_2$	4-CH_3Ph-;4′-ClPh	1	60	2	93
23	4-CH_3OCPhBr	4-ClPhB$(OH)_2$	4-CH_3OCPh-;4′-ClPh	1	60	2	98
24	4-OHCPhBr	4-ClPhB$(OH)_2$	4-OHCPh-;4′-ClPh	1	60	2	97

Reaction conditions: ArBr (1.0 mmol), $ArB(OH)_2$ (1.2 mmol), K_2CO_3 (2.0 mmol), DMF: H_2O = 4 ml: 1 ml, under aerobic atmosphere. The molar ratio of Ligand (1 mol%) and Pd (1 mol%) is 1:1.

[a]Isolated yield.

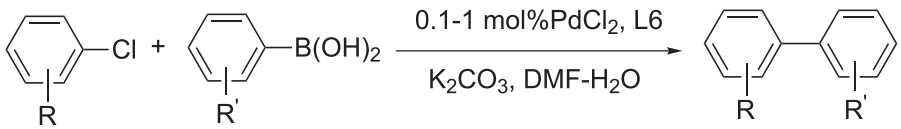
[b]Under nitrogen atmosphere.

The reaction conducted with a lower catalytic loading was also explored. It was shown that the catalytic system was still effectively able to convert substrates such as 4-bromotoluene and 2-bromotoluene into the corresponding product in excellent yield when the catalyst loading was decreased to 0.5 mol% (Table 3, runs 8 and 16). It is important to note that a high yield of 90% was received in the case of 4-bromotoluene as substrate at 0.1 mol% palladium (Table 3, run 9). In contrast, the cross-coupling of 2-bromotoluene with phenylboronic acid resulted in remarkably lower yields (20%) at 0.1 mol% palladium loading, which suggest that steric demanding substrates require higher catalytic loading to achieve satisfactory yields. Moreover, very low activities were investigated when the catalyst was decreased to 0.01 mol% (Table 3, runs 10 and 18).

Based on the successful couplings of most bromide substrates with phenylboronic acid, other arylboronic acids such as 2-methylphenylboronic acid and 4-chlorophenylboronic acid were introduced as coupling partners. Under the effective **L6**/$PdCl_2$ catalytic system, aryl bromides with electron-donating functional groups, 4-bromoanisole (Table 3, run 20), together with 1-bromo-4-*tert*-butylbenzene (Table 3, run 21), were coupled very successfully with 2-methylphenylboronic acid in almost quantitative yields. Moreover, some representative types of aryl bromides also provided their coupling products with 4-chlorophenylboronic acid in high yields (Table 3, runs 22–24).

Inspired by the results derived from the cross-couplings of aryl bromides with arylboronic acids, we carried out further investigations on catalytic studies on more challenging aryl chlorides with arylboronic acids. Aryl chlorides are widely utilized in cross-coupling reactions owing to their commercial availability but are notoriously known for difficult activation of the C-;Cl bond.[67,68] In this study, both activated and deactivated aryl chlorides were tested in the presence of **L6** and the results are listed in Table 4. Temperature and reaction times consumed in the couplings of the aryl chlorides were much higher and longer, mainly resulting from the commonly recognized hard activation of inert aryl chlorides. As depicted, aryl chlorides with electron-withdrawing groups, such as 4-chloronitrobenzene (Table 4, run 1), 2- and 4-chlorobenzonitriles (Table 4, runs 2 and 4) proceeded at 110°C to give their products in more than 90% yield in 4–6 h. Meanwhile, 4-chlorobenzaldehyde also yielded the product in 85% at the same reaction temperature (Table 4, run 6). However, the analogous activated substrate 2-chloronitrobenzene (Table 4, run 8) gave a much lower yield of 56%. We carefully checked the reaction and found that dehalogenation and homocoupling of 2-chloronitrobenzene occurred during the process and side products were detected. In addition, the low transformation yield of 4-chloroacetophenone was mainly due to its dehalogenation in the reaction (Table 4, run 9, 26% yield).[69,70] Nevertheless, activated aryl chlorides were much easier to couple with arylboronic acids. For example, 4-chlorobenzaldehyde underwent coupling with 4-chlorophenylboronic acid, 2-methylphenylboronic acid and 4-methylphenylboronic acid in 89%, 91% and 96% yield, respectively (Table 4, runs 10–12). Moreover, it is noteworthy that 2-chlorobenzonitrile could couple with 4-methylphenylboronic acid to proceed to conversion at 71% yield to provide an important intermediate of the synthesis of the sartan family, which is an active ingredient in antihypertensive drugs (Table 4, run 13). On the other hand, cross-coupling between deactivated aryl chlorides and arylboronic acids also afforded moderate yields. For example, the corresponding product of 4-chlorotoluene with phenylboronic acid was obtained in 52% yield (Table 4, run 14) while 4-chloroanisole yielded 31% (Table 4, run 15), which might be ascribed to their obvious low activities of substrate. Moreover,

Table 4. Suzuki–Miyaura cross-coupling reaction of aryl chlorides with phenylboronic acid under aerobic conditions



Run	Ar-;Cl	$ArB(OH)_2$	Product	Pd (mol%)	*t* (h)	Yield (%)[a]
1	4-O_2NPhCl	$PhB(OH)_2$	4-O_2NPh-;Ph	1	6	95
2	2-NCPhCl	$PhB(OH)_2$	2-NCPh-;Ph	1	4	94
3	2-NCPhCl	$PhB(OH)_2$	2-NCPh-;Ph	0.5	6	35
4	4-NCPhCl	$PhB(OH)_2$	4-NCPh-;Ph	1	4	92
5	4-NCPhCl	$PhB(OH)_2$	4-NCPh-;Ph	0.5	6	61
6	4-OHCPhCl	$PhB(OH)_2$	4-OHCPh-;Ph	1	6	85
7	4-OHCPhCl	$PhB(OH)_2$	4-OHCPh-;Ph	0.5	8	67
8	2-O_2NPhCl	$PhB(OH)_2$	2-O_2NPh-;Ph	1	6	56
9	4-CH_3OCPhCl	$PhB(OH)_2$	4-CH_3OCPh-;Ph	1	4	26
10	4-OHCPhCl	4-ClPh$B(OH)_2$	4-OHCPh-;4′-ClPh	1	8	89
11	4-OHCPhCl	2-CH_3PhB(OH)2	4-OHCPh-;2′-CH_3Ph	1	12	91
12	4-OHCPhCl	4-CH_3Ph$B(OH)_2$	4-OHCPh-;4′-CH_3Ph	1	8	96
13	2-NCPhCl	4-CH_3Ph$B(OH)_2$	2-NCPh-;4′-CH_3Ph	1	8	71
14	4-CH_3PhCl	$PhB(OH)_2$	4-CH_3-;Ph	1	6	52
15	4-CH_3OPhCl	$PhB(OH)_2$	4-CH_3-;OPh-;Ph	1	4	31

Reaction conditions: ArcCl (1.0 mmol), $ArB(OH)_2$ (1.2 mmol), K_2CO_3 (2.0 mmol), DMF:H_2O = 4:1 ml; reaction temperature 110°C, under aerobic atmosphere. Molar ratio of ligand (1 mol%) to Pd (1 mol%) is 1:1.

[a]Isolated yield.

a decreasing catalyst loading was also investigated, and it was found that much lower yields were obtained, even with longer reaction times (Table 4, runs 3, 5 and 7). These results indicate that a appropriate catalyst loading was 1 mol% relative to aryl chlorides.

Conclusions

A series of pyridylbenzamidine ligands were synthesized and characterized. The ligands were successfully employed in the palladium-catalyzed Suzuki–Miyaura reaction. It was shown that the bulky steric and electron-donating substituents on ligands favored cross-coupling. In particular, the experimental data shows that the methyl substituent at the *ortho* position of the pyridine nitrogen is facilitated for the cross-coupling reaction. Under optimized reaction conditions, a significant advance in the efficiency of cross-coupling of aryl bromides and aryl chlorides with arylboronic acids to give desired biaryls was demonstrated.

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Appendix

Crystallographic data for the structural analysis of **L3PdCl$_2$** have been deposited with the Cambridge Crystallographic Data Centre as CCDC 861946. Copies of this information can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or http://ccdc.cam.ac.uk), upon request.