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$Pd(CH_3CN)_2Cl_2$/Pipecolinic Acid as a Highly Efficient Catalytic System for Suzuki-Miyaura Cross-coupling Reaction of Bromoaryl Carboxylic Acids in Water

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Abstract: In this study, a convenient and highly efficient catalytic system for the Suzuki-Miyaura coupling reaction was investigated under mild conditions. A combination of $Pd(CH_3CN)_2Cl_2$ and pipecolinic acid showed excellent catalytic performance and afforded high turnover numbers; turnover numbers were up to 4.9×10^5 for the coupling reaction of 4-bromobenzoic acid and tetraphenylboron sodium. The catalytic system was also effective for the indexes of 4-bromobenzoic acid, and high turnover numbers were obtained.

Keywords: N–O ligand; Suzuki-Mayaura coupling; palladium; pipecolinic acid

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1. Introduction

The C–C cross-coupling reaction, which is usually catalyzed by transition metals such as palladium [1] and gold [2,3], provides a powerful method for obtaining a biaryl scaffold. Among these catalysts, palladium is the most widely used, showing highly efficient catalytic performance. Impressive progress has been obtained in the enhancement of the catalytic performance of palladium in past decades [4]. However, obtaining a highly efficient catalyst under room temperature conditions with no use of hazardous and expensive organic solvents still remains challenging. Nitrogen ligands have been used to complex and stimulate the palladium species instead of phosphine ligands, and excellent results have been reported [5–20]. Most nitrogen ligands are stable in air and are easily available, which reveals their usefulness and appearance as a pertinent alternative. Primary, secondary, and tertiary amines have served as ligands to stimulate the palladium-catalyzed Suzuki-Miyaura coupling reaction of aryl halides and arylboronic acids [4–6]. $Pd(OAC)_2$/DABCO (triethylenediamine) has been reported as an efficient catalytic system for the Suzuki-Miyaura cross-coupling of *p*-nitroiodobenzene and phenylboronic acid, with turnover numbers (TONs) of up to 900,000 [7]. However, 0.01–2 mol% of $Pd(OAC)_2$/DABCO should be used to obtain a high yield in the coupling reaction of aryl bromides and phenylboronic acid. Recently, a ppm level of $PdCl_2$ has been developed for the Suzuki-Miyaura coupling reaction and in this process high-pressure and high-temperature water is necessary in order to gain a high yield [21]. Amino acid complexes show good catalytic performance in C–C bond and C–N formation [18–20,22,23]. Previous work has shown that $Pd(NH_2CH_2COOH)_2Cl_2$ can catalyze the cross-coupling reaction. In order to obtain a high yield of the coupling products, 0.01–1 mol% Pd is necessary [23]. Hence, pipecolinic acid, a kind of amino acid, was chosen as a ligand for the Pd-catalyzed Suzuki-Miyaura coupling reaction at room temperature in water, and a ppm level of Pd was enough to gain a high yield.

2. Results and Discussions

2.1. Optimization of Catalytic Conditions

The catalytic activities of $Pd(CH_3CN)_2Cl_2$/L1–L3 in the Suzuki-Miyaura cross-coupling reaction were tested (Figure 1). The coupling reaction of 4-bromobenzoic acid and tetraphenylboron sodium was chosen as the model coupling reaction (Figure 1). The stimulation of the ligands (L1–L3) for the Pd-catalyzed cross-coupling reaction was evaluated. When 0.002 mol% $Pd(CH_3CN)_2Cl_2$ was used solely as the catalyst, 4.9% of the corresponding coupling product was detected by high performance liguid chromatography (HPLC) (Table 1, Entry 1). L1 was discovered as being able to trigger the cross-coupling reaction (Table 1, Entry 4) but $Pd(CH_3CN)_2Cl_2$/L2 and L3 showed poor catalytic activity within the cross-coupling reaction. A brown precipitate was formed when $Pd(CH_3CN)_2Cl_2$/L2 or $Pd(CH_3CN)_2Cl_2$/L3 was placed in water for about 20 minutes. The instability of the combination of Pd $(CH_3CN)_2Cl_2$/L2 or Pd $(CH_3CN)_2Cl_2$/L3 in water may be the main reason for their poor catalytic performance.

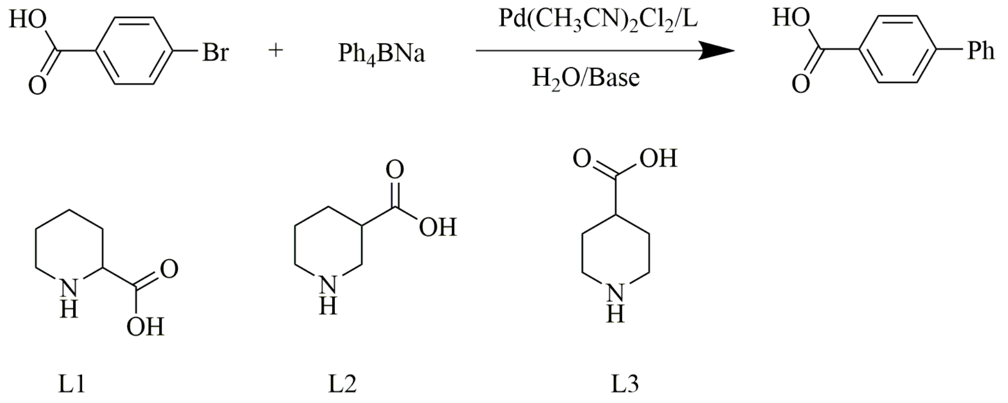


Figure 1. Pd-catalyzed Suzuki-Miyaura cross-coupling reaction of 4-bromobenzoic acid and tetraphenylboron sodium.

Table 1. Optimization of reaction conditions.

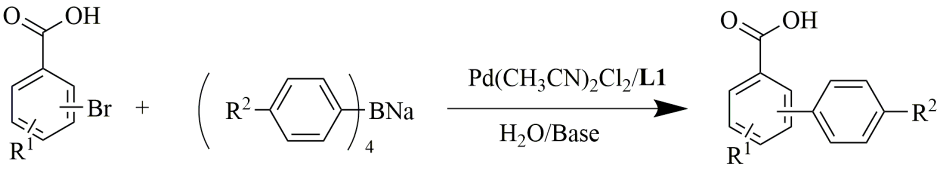
Entry [a]	Ligand	Pd (mol%)	Base	Time (h)	Yield [e] (%)	TON [f]
1	-	0.002	Na_2CO_3	22	4.9	-
2	L2	0.002	Na_2CO_3	22	6.9	-
3	L3	0.002	Na_2CO_3	22	4.0	-
4	L1	0.002	Na_2CO_3	6	95	4.7×10^4
5	L1	0.002	$NaHCO_3$	6	94	4.7×10^4
6	L1	0.002	NaF	6	24	1.2×10^4
7	L1	0.002	NaOH	6	84	4.2×10^4
8	L1	0.004	Na_2CO_3	6	99	2.5×10^4
9	L1	0.0002	Na_2CO_3	6	24	1.2×10^5
10	L1	0.0002	Na_2CO_3	22	97	4.9×10^5
11 [b]	L1	0.0002	Na_2CO_3	22	8.2	-
12 [c]	L1	0.0002	Na_2CO_3	22	7.5	-
13 [d]	L1	0.0002	Na_2CO_3	22	<5	-

[a] Reaction conditions: mole ratio (ligand:$Pd(CH_3CN)_2Cl_2$) = 2:1, 1.0 mmol 4-bromobenzoic acid, 0.255 mmol tetraphenylboron sodium, 2.5 mmol base, 4 mL H_2O, room temperature, ambient conditions. [b] Reaction conditions: 1.0 mmol 4-bromobenzoic acid, 1.2 mmol phenylboronic acid. [c] Reaction conditions: 1.0 mmol 4-bromobenzoic acid, 1.2 mmol potassium phenyltrifluoroborate. [d] Reaction conditions: 1.0 mmol bromobenzene, 0.255 mmol tetraphenylboron sodium. [e] Detected by HPLC, with benzoic acid used as an internal standard. [f] Turnover number (TON): mole ratio of product with catalyst.

The next step was to optimize the reaction conditions. As known, the base plays an important role in the Suzuki-Miyaura coupling reaction, so the effects of various inorganic bases on the coupling reaction were investigated first. Ninety-five percent (TON = 4.7×10^4) of the corresponding cross-coupling product was obtained when the coupling reaction proceeded for 6 h using 0.002 mol% $Pd(CH_3CN)_2Cl_2$, 0.004 mol% L1, and 2.5 equiv of Na_2CO_3 in water at room temperature, whereas in the presence of 2.5 equiv of NaF or NaOH, the yield decreased to 24% and 84%, respectively (Table 1, Entry 4,5,7). Under similar conditions, when 2.5 equiv of $NaHCO_3$ was used, a yield identical to that using Na_2CO_3 was obtained (Table 1, Entry 6). When the amount of catalyst increased to 0.004 mol%, an almost equivalent amount of cross-coupling product was obtained after 6 h (Table 1, Entry 8). A 24% (TON = 1.2×10^5) yield was observed after 6 h when the amount of catalyst decreased to 0.0002 mol% (Table 1, Entry 9), whereas, as the reaction time was extended to 22 h, a 97% (TON = 4.9×10^5) yield of the cross-coupling product was obtained (Table 1, Entry 10). $Pd(CH_3CN)_2Cl_2$/**L1** showed high catalytic activity at low catalytic loading. At low catalytic loading, the cross-coupling reaction of phenylboronic acid or potassium phenyltrifluoroborate and 4-bromobenzoic acid could occur efficiently (Table 1, Entry 11,12). Under the same conditions, no cross-coupling product was isolated when bromobenzene reacted with tetraphenylboron sodium catalyzed by 0.0002 mol% $Pd(CH_3CN)_2Cl_2$/L1 (Table 1, Entry 13).

2.2. Evaluation of the Scope of $Pd(CH_3CN)_2Cl_2$ /L1

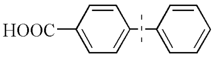
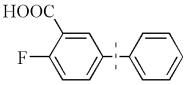
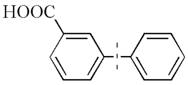
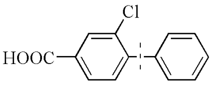
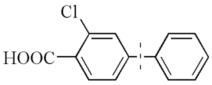
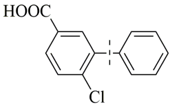
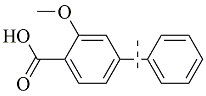
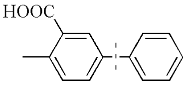
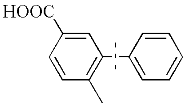
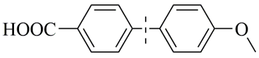
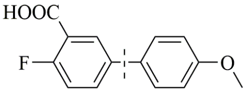
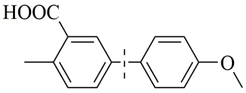
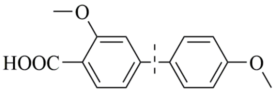
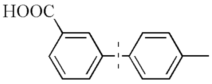
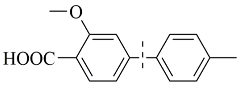
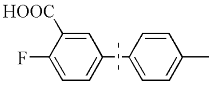
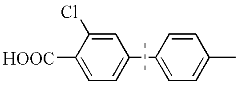
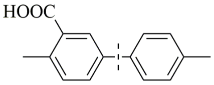
The catalytic system $Pd(CH_3CN)_2Cl_2$/**L1** was also applied to various substrates (Figure 2), the results of which are shown in Table 2. At lower catalytic loading, such as at 0.002 mol%, $Pd(CH_3CN)_2Cl_2$/**L1** was exceptionally active for the Suzuki-Miyaura cross-coupling of various brominated aromatic carboxylic acids and tetraarylboron sodium. Using this system, high yields could be obtained for the coupling reactions of bromide aromatic carboxylic acids with electron-withdrawing and electron-donating substituents and tetraphenylboron sodium (Table 2, Entry 1–9). *Ortho*-substituted brominated aromatic carboxylic acids and tetraarylboron sodium reacted smoothly, though the yield of the corresponding coupling compounds slightly decreased (Table 2, Entry 4,6,9). This indicates that the steric hindrance of coupling partners had less influence on this Suzuki-Miyaura coupling reaction. Tetraarylboron sodium bearing methyl or methoxy groups converted to the corresponding products at high yield (Table 2, Entry 10–18).



R^1=-H, -F, -Cl, -CH_3, -OCH_3
R^2=-H, -CH_3, -OCH_3

Figure 2. Suzuki-Miyaura cross-coupling reaction catalyzed by $Pd(CH_3CN)_2Cl_2$/L1.

Table 2. The scope of the Pd-catalyzed Suzuki-Miyaura cross-coupling reaction.

Entry [a]	Halide Fragment	Tetraarylboron Sodium Fragment	Yield [d] (%)	TON [e]
1			95(96)	4.8 × 10^4
2 [b]			98(97)	4.9 × 10^4
3			85(72)	4.3 × 10^4
4			96(98)	4.8 × 10^4
5			99(96)	5.0 × 10^4
6			86(75)	4.3 × 10^4
7			99(97)	5.0 × 10^4
8			98(94)	4.9 × 10^4
9			74(40)	3.7 × 10^4
10			95(90)	4.8 × 10^4
11 [b]			93(92)	4.8 × 10^4
12			94(95)	4.8 × 10^4
13			82(73)	4.1 × 10^4
14			96(90)	4.8 × 10^4
15 [c]			99(95)	5.0 × 10^4
16 [b,c]			90(80)	4.5 × 10^4
17 [c]			97(94)	4.9 × 10^4
18 [c]			88(70)	4.4 × 10^4

[a] Reaction conditions: 1.0 mmol brominated aromatic carboxylic acid, 0.025 mmol tetraarylboron sodium, 2.5 mmol Na_2CO_3, 4.0 mL H_2O, 2.0 × 10^{-5} mmol $Pd(CH_3CN)_2Cl_2$, 4.0 × 10^{-5} mmol **L1**, 24 h, room temperature, ambient conditions. [b] 2.5 mmol Na_3PO_4 was used as a base. [c] 2 mL H_2O/2 mL CH_3CH_2OH was used as a solvent. [d] Both HPLC yields and isolated yields of the coupling products were tested. [e] TON: mole ratio of product with catalyst.

3. Materials and Methods

3.1. Materials

Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Brominated aromatic carboxylic acids were recrystallized from a mixture of water and ethanol before being used. NMR (nuclear megnetic reonance) spectroscopy was performed on a Brucker spectrometer operating at 400MHz (^{1}H NMR) and 100MHz (^{13}C NMR) with DMSO-d_6 as the solvent and TMS as the internal standard. The reaction mixtures were analyzed by HPLC (FL2200, FuLi Instrument) using a C-18 column.

3.2. Methods

General Suzuki-Miyaura Cross-Coupling Procedure: a typical experimental procedure for the Suzuki-Miyaura cross-coupling reaction of brominated aromatic carboxylic acid and tetraphenylboron sodium catalyzed by 0.0002 mol% $Pd(CNCH_3)_2Cl_2$ and 0.0004 mol% pipecolinic acid.

Firstly, $Pd(CNCH_3)_2Cl_2$ (6.5 mg, 0.025 mmol) and pipecolinic acid (6.4 mg, 0.050 mmol) were dissolved in 50 mL of ethanol and the resulting mixture stirred for 4 h till a yellow solution was obtained. The solvent was removed under vacuum. Subsequently, 50.00 mL deionized water was added and a yellow solution was obtained. The solution was diluted to 1.00×10^{-4} mmol/mL with deionized water. Then, 0.20 mL Pd-catalyst solution (1.00×10^{-4} mmol/mL) was added to a mixture of brominated aromatic carboxylic acid (1.0 mmol), tetraphenylboron sodium (0.0255 mmol), Na_2CO_3 (2.5 mmol), and 3.8 mL deionized water in a tube. The mixture was stirred under ambient conditions for 22 h. After this, 5% of HCl was added till the $pH < 3$. The precipitate was filtered using a vacuum pump and then dissolved in methanol and analyzed by HPLC. The isolated coupling products were recrystallized from ethanol (50%) and analyzed via NMR spectrum. The ^{1}H NMR and ^{13}C NMR data of coupling products were shown in the Supplementary Materials.

4. Conclusions

In conclusion, in this study a $Pd(CH_3CN)_2Cl_2$/pipecolinic acid catalyst for the Suzuki-Miyaura cross-coupling reaction has been reported. The catalyst exhibited highly efficient catalytic performance for the coupling of 4-bromobenzoic acid and tetraphenylboron sodium under mild conditions with a ppm level of Pd (0.0002 mol% Pd). $Pd(CH_3CN)_2Cl_2$/pipecolinic acid proved to be efficient for the synthesis of various substituted biaryl acids under mild conditions with 0.002 mol% Pd.

Supplementary Materials: The following are available online at http://www.mdpi.com/2073-4344/9/1/86/s1, analytical data and NMR spetrum for all compound.

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Conflicts of Interest: The authors declare no conflict of interest.

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